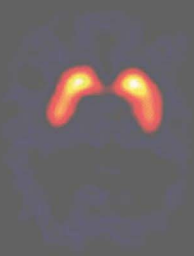

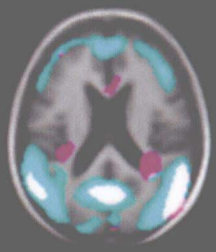

COGNITIVE IMPAIRMENT AND DEMENTIA IN PARKINSON'S DISEASE

SECOND EDITION

EDITED BY
MURAT EMRE

OXFORD

Cognitive impairment and dementia in Parkinson's disease

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UNIVERSITY PRESS

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Great Clarendon Street, Oxford, OX2 6DP,
United Kingdom

Oxford University Press is a department of the University of Oxford.
It furthers the University's objective of excellence in research, scholarship,
and education by publishing worldwide. Oxford is a registered trade mark of
Oxford University Press in the UK and in certain other countries

First Edition published in 2010
Second Edition published in 2015

Impression: 1

Published in the United States of America by Oxford University Press
198 Madison Avenue, New York, NY 10016, United States of America

British Library Cataloguing in Publication Data

Data available

Library of Congress Control Number: 2014946888

ISBN 978–0–19–968164–8

Printed and bound by
CPI Group (UK) Ltd, Croydon, CR0 4YY

Cognitive impairment and dementia in Parkinson's disease

Preface to the second edition

The first edition of *Cognitive impairment and dementia in Parkinson's disease* was published 5 years ago. The book was well received by the scientific community, confirming that it filled a gap and satisfied an unmet need.

The first publication of the book proved to be timely. Since then, the topic of cognitive impairment and dementia in Parkinson's disease has become increasingly popular, and there have been a number of developments in the field, including new data on the natural course, clinical features, pathological correlates, neuroimaging, and treatment of this condition. Hence, we decided to work on a new edition of the book which would include these recent developments. All the authors of the original chapters kindly agreed to revise their contributions to reflect the new findings; I am very grateful to them. In the meantime, mild cognitive impairment in Parkinson's disease has been better recognized, criteria for its diagnosis have been published, and there has also been increasing interest in biomarkers of cognitive dysfunction and dementia. We decided to include several new chapters covering these topics.

We hope that the new edition of the book will be as useful for the scientific community as the previous one and that it will continue to serve as a major reference source for cognitive impairment and dementia in Parkinson's disease.

Murat Emre
İstanbul, December 2014

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Chapter 1

Introduction

Murat Emre

James Parkinson was more than a physician. One of his biographers records that 'Like many of his contemporaries he had absorbing and overwhelming interests which ranged successively, and successfully, through politics, the church, medicine and geology' and that 'James was a careful, perhaps obsessional, man' [1]. He had many intellectual skills, but above all he was a sharp and succinct observer, which enabled him to find associations no one had described before, resulting in discoveries and descriptions in medicine, geology, and palaeontology which still bear his name. Yet Parkinson's *An essay on the shaking palsy*, which otherwise so succinctly described the features of the disease that was later named after him, almost completely dismissed its mental aspects. He described the characteristic features of the disease as 'Involuntary tremulous motion with lessened muscular power, in parts not in action and even when supported, with a propensity to bend the trunk forwards and to pass from a walking to a running pace: the senses and intellects being uninjured' [2]. This statement, 'senses and intellects being uninjured', was probably one of the main reasons why mental dysfunction in Parkinson's disease (PD) was ignored for a long time to come, although his general description of the final stages of the disease ends with the statement that 'The urine and faeces are passed involuntarily; and at the last, constant sleepiness, with slight delirium, and other marks of extreme exhaustion, announce the wished-for release'. This brief statement on likely mental dysfunction attracted little attention as it was rather equivocal. Parkinson was honest about the potential shortcomings of his descriptions, as he admits in the opening remarks in his Preface: 'it therefore is necessary, that some conciliatory explanation should be offered for the present publication: in which, it is acknowledged, that mere conjecture takes the place of experiment; and, that analogy is the substitute for anatomical examination, the only sure foundation for pathological knowledge'. He realized that early and late stage symptoms may be different, stating that:

> The disease is of long duration: to connect, therefore, the symptoms, which occur in its later stages with those which mark its commencement, requires a continuance of observation of the same case, or at least a correct history of its symptoms, even for several years. Of both these advantages the writer has had the opportunities of availing himself; and has hence been led particularly to observe several other cases in which the disease existed in different stages of its progress.

Parkinson was a modest and unassuming man; true to form, he ended his opening remarks as follows: 'Should the necessary information be thus obtained, the writer will repine at no censure which the precipitate publication of mere conjectural suggestions may incur; but shall think himself fully rewarded by having excited the attention of those, who may point out the most appropriate means of relieving a tedious and most distressing malady'. He did excite attention for decades to come, for which he received well-deserved credit and recognition. His concluding remarks were exemplary and constitute a timely reminder for all contemprorary clinical scientists: 'Before concluding these pages, it may be proper to observe once more, that an important object proposed

to be obtained by them is, the leading of the attention of those who humanely employ anatomical examination in detecting the causes and nature of diseases, particularly to this malady. By their benevolent labors its real nature may be ascertained and appropriate modes of relief, or even cure, pointed out'.

Why would such an excellent observer miss or ignore the mental aspects of the disease? The reasons are probably rather simple: James Parkinson did not observe a large number of patients—his essay was based on the study of only six. Two of them were 'casually met with in the street' (one aged 62 and the other about 65), questioned and observed once, while for a third case 'the particulars of which could not be obtained, and the gentleman, the lamented subject of which was only seen at a distance'. He personally attended to the other three patients, two of them in their 50s, and the third was examined at the age of 72, with a disease duration ranging from about 5–12 years. One of these patients was lost to follow-up after the first examination, and probably only one was followed to his terminal stages. Of particular note is that five of his six cases were seen at a relatively young age. We now know that age is the most important risk factor for dementia and that it rarely occurs in patients below the age of 60 years.

In fact, the occurrence of cognitive dysfunction and dementia in some patients with what came to be known as PD was recognized shortly after the description by Parkinson himself. Charcot, who in his *Lectures on diseases of the nervous system* (1877) called the disease 'maladie de Parkinson', stated that 'at a given point, the mind becomes clouded and the memory is lost'. Together with Vulpian, Charcot had already referred to these aspects of the disease during 1861–2: 'in general, psychic faculties are definitely impaired'. Nevertheless these statements attracted little attention, and for many years PD was perceived to be a pure motor disorder.

As patients with PD survived for substantially longer with modern dopaminergic treatment, cognitive dysfunction and dementia became more apparent. Descriptions from the 1960s onwards pointed out that dementia may accompany PD. Even then, it was assumed that dementia in PD (PD-D) may be a consequence of the ageing process, as ageing was recognized to be the main risk factor for PD-D. The observation that PD-D is frequently accompanied by Alzheimer's disease (AD)-type pathology, in particular plaques, subsequently led to the contention that PD-D simply represents coincident AD. This perception delayed the recognition of PD-D as a separate entity. Subsequently, however, prospective epidemiological studies clearly demonstrated that both the prevalence and incidence of dementia in PD are substantially increased compared with age-matched controls, indicating that dementia was related to the disease pathology itself. With the refinement of neuropsychological methods and an understanding of the circuits subserving discrete mental processes, the clinical profile of PD-D was better worked out in comparative studies, demonstrating the differences between PD-D and AD. In parallel, comprehensive clinicopathological studies were conducted, which gained particular momentum after the discovery that α-synuclein is the main component of Lewy bodies (LB). The development of immunohistochemistry using antibodies against this protein, which turned out to be more sensitive in detecting LB-type pathology than the conventional ubiquitin staining, was crucial in dissecting out the underlying pathology. All these developments were instrumental in the recognition of PD-D as a separate entity and dementia as an integral part of the disease spectrum of PD.

The consequences of considering dementia as part of the pathological substrate of PD are not only academic. As PD patients survive for longer due to more efficient treatment for their motor symptoms, cognitive deficits and dementia occur more often and constitute one of the main reasons for severe disability in the later stages of the disease. These deficits are not responsive to dopaminergic substitution and often worsen under such treatment. Hence, understanding and managing all aspects of PD-D are of practical relevance for patients and their families. Full

recognition of its clinical features would allow accurate diagnosis as well as development of assessment measures to evaluate the natural course of the disease and the potential benefits of future treatments. Understanding the associated biochemical deficits, pathophysiology, and pathology would allow such potential treatments to be developed.

Much has already been achieved. Major epidemiological studies have produced valuable data about the point prevalence, cumulative incidence, and risk factors associated with PD-D. A number of clinical studies have been able to discern the profile of cognitive deficits and the frequency as well as the spectrum of accompanying behavioural symptoms. Comprehensive clinico-pathological correlation studies have successfully described the type and topography of the underlying pathology, and genetic findings have provided data supporting the role of α-synuclein. Finally, specific clinical diagnostic criteria have been published and the first specific treatment has become available.

The purpose of this book is to compile in one volume the data that have accumulated over the course of the last few decades. Physicians treating patients with PD will be able to find information on all aspects of the disease without the need for time-consuming searches. It is also hoped that this book could lead to more interest in PD-D, giving rise to new ideas and research initiatives. It would be appropriate to echo James Parkinson's concluding remarks: the editor and the authors of this book would feel fulfilled and satisfied if this latter purpose is served.

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