Handbook of Movement Disorders

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HANDBOOK

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Professor Chaudhuri is the author of 172 papers including reviews and book chapters, co-editor of four books on Parkinson's disease and restless legs syndrome (two in press), and has published over 150 peer reviewed abstracts. He has contributed extensively to educational radio and television interviews, newspaper articles and videos. He has also lectured extensively on PD and restless legs syndrome at international meetings in Japan, continental Europe, India and Australia. His major research interests are drug treatment of PD and restless legs syndrome, Parkinsonism in minority ethnic groups within the UK and abroad and sleep problems in PD. In 2005 he was awarded the DSc degree by the University of London and he received his personal Chair in neurology in 2007.

William G Ondo is Professor of Neurology at Baylor College of Medicine, as well as associate director at the Parkinson's Disease Center and Movement Disorders Clinic in Houston, Texas. His medical degree was awarded by the Medical College of Virginia (Richmond, Virginia), and he completed an internship at the University of North Carolina Hospital (Chapel Hill, North Carolina) and a neurology residency at Duke University (Durham, North Carolina). In 1995, Professor Ondo undertook a Movement Disorders fellowship with Dr Jankovic and joined the Baylor faculty the following year. Professor Ondo maintains membership in multiple professional associations and research groups, which include the American Neurological Association, the American Academy of Neurology, and multiple study groups. He is also a diplomate of the American

Board of Psychiatry and Neurology. Professor Ondo is interested in all areas of adult and pediatric movement disorder research and has served as primary, treating, and sub-investigator for many research projects involving those disease states. He has authored more than 200 original articles, review articles, and book chapters, and has edited two test books on movement disorders. He has also served on numerous editorial boards, speaker bureaus, study groups, and has lectured widely. His current research interests include Parkinson's disease, restless legs syndrome, tremor and the use of botulinum toxins.

Kartik Logishetty graduated from Imperial College London in surgery and anaesthesia, and is currently completing his medical training at King's College London. He is a clinical research assistant in Parkinson's Disease, particularly focusing on the recognition and treatment of non-motor symptoms, at the National Parkinson Foundation Centre of Excellence at King's College Hospital, London.

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Rosalie Sherman graduated from Cambridge University in medical sciences. She is currently pursuing a career in medicine with a special interest in neurology and movement disorders and is currently actively involved in research as part of the Parkinson's Disease Non-Motor Group at the NPF Centre of Excellence at King's College Hospital, London.

Preface

Movement disorders are a complex group of disorders spanning all aspects of neurological illnesses and range from conditions characterized by too little movement (hypokinesis) to those where movement is excessive (hyperkinesis). The classic example would be Parkinson's disease, while other movement-related problems, such as tremor, chorea, dystonia, myoclonus, hemiballism and tics, occur in a range of inherited, drug-induced and sporadic disorders. Genetics plays an important part in the genesis of several conditions characterized by various movement disorders, such as Huntington's disease, dystonic conditions and myoclonus. Somatization from psychologically determined conditions can also manifest as movement disorders. Finally, sleep may be affected by movement disorders and a typical example would be restless legs syndrome.

To non-experts, movement disorders may appear to be complex, sometimes bizarre and difficult to manage. Diagnosis is based mostly on observation and examination rather than radiology and serological assessments. This comprehensive handbook deals with all the above movement disorders in a holistic manner, providing a detailed "snapshot" view of these complex disorders. As well as being useful to the general physician working in clinical settings where movement disorders often first present, such as accident and emergency departments or in primary care, we hope that the up-to-date information will be useful for trainees and experts in the field of movement disorders.

Chapter 1

Parkinson's disease

Kartik Logishetty and K Ray Chaudhuri

Introduction

Parkinson's disease was first described by the London physician, James Parkinson, in 1817 and later named after him by Charcot. Parkinson's disease is one of the most important disabling illnesses of later life. The characteristic tremor, posture and clinical course were first depicted by James Parkinson in his essay *The Shaking Palsy* in 1817; our description today has added rigidity and bradykinesia to the list of primary symptoms. The modern concept of Parkinson's disease also includes a range of nonmotor symptoms (NMS), some of which (eg, olfactory deficit) could pre-date the motor diagnosis by 1–5 years [1].

Epidemiology, incidence, and prevalence

Currently, there is no "in-life" marker for idiopathic Parkinson's disease and estimates of prevalence and incidence are somewhat inexact. It is estimated to affect 1% of 70 year olds, but it is also seen in younger people, with 10% of cases occurring before the age of 50 [2,3]. Estimates of the annual incidence of Parkinson's disease are in the range of 4–20 per 100,000 individuals. A widely accepted figure for the prevalence of Parkinson's disease is approximately 200 per 100,000 population. In the UK, there are approximately 120,000–130,000 diagnosed cases, but there may be many more that remain undiagnosed. In the USA, it is estimated that between 750,000 and 1.5 million people have the condition [2,4]. Both the incidence and prevalence of Parkinson's disease increase with age, and the prevalence may be as high as 1 in 50 for patients over the age of 80 years. Men are 1.5 times more likely than women to develop the condition. Hospital-based studies have suggested that Parkinson's disease is less common in the Black population, although this observation remains controversial.

Risk factors

In spite of considerable research, it remains difficult to identify the population at risk for Parkinson's disease. The aging process can accelerate the development of Parkinson's disease but is not solely responsible, as some patients develop the disease early in life [5]. Furthermore, the pattern of dopamine cell loss in normal aging differs from that in Parkinson's disease. Certain personality traits and environmental factors may increase the risk of Parkinson's disease but the evidence for this is not robust. People with a family history of Parkinson's disease, particularly in first-degree relatives, are also at higher risk of developing the disease.

It has been postulated that people may be affected differently by a combination of genetic and environmental factors. 1-Methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP), accidentally consumed as a heroin contaminant in the USA in the late 1970s and early 1980s, caused an outbreak of levodopa-responsive parkinsonism [3]. This led to the development of MPTP as an experimental agent to cause selective nigrostriatal cell loss in animal models. It has been recently recognized that welders have an increased incidence of parkinsonism, suggesting that manganese is a causative factor. There have been conflicting reports about other environmental agents that may predispose a person to Parkinson's disease (Figure 1.1).

Genetic factors

Individuals with a positive family history have twice the risk of developing Parkinson's disease, and the risk for siblings is increased significantly if there is an affected sibling with young-onset Parkinson's disease. The risk increases further to 12–24% if both a sibling and a parent are affected.

Mapping and cloning of genes have shown that Parkinson's disease is in fact a heterogeneous group of diseases associated with a spectrum of clinical and pathological changes.

Personality and environmental toxin-based risk factors for Parkinson's disease
Obsessive–compulsive personality disorder
Major depression
Drinking well water
Insecticide/pesticide exposure
Manganese exposure (welding)
MPTP exposure

Figure 1.1 Personality and environmental toxin-based risk factors for Parkinson's disease. MPTP, 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

In 1996, Polymeropoulos et al. [6] determined that a mutation in the gene coding for the protein α-synuclein (a key component of Lewy bodies) caused an aggressive parkinsonism in a multi-generation Italian–American family; this gene was named *PARK1*. Thirteen genetic loci (denoted *PARK1–13*) have now been implicated in rare forms of Parkinson's disease (Figure 1.2), and at least six of these have been reported to be carried by family members. In addition to "causative" Parkinson's disease genes, analysis has tentatively identified several "susceptibility" loci, including mitochondrial genes coding for proteins involved in the electron transport chain, genes encoding the protein "tau", and *NR4A2*, which is essential for nigral dopaminergic neuron differentiation. *PARK2* (parkin) and *LRRK2* genes are the most prevalent causative genes. *LRRK2* (leucine-rich repeat kinase 2) is part of the family of *ROCO* genes, and encodes for the protein dardarin. *LRRK2* has been associated with both familial and sporadic late-onset Parkinson's disease. G2019S is the most common *LRRK2* substitution, which accounts for 0.5–2% of apparently "sporadic" cases and approximately 5% of familial cases; it is identified more frequently in North African Arabs and Ashkenazi Jews. In the Asian Chinese population the G2385R mutation variant is seen. In Ashkenazi Jews, mutations in the glucocerebrosidase (*GBA*) gene have been reported to confer susceptibility to Parkinson's disease, whereas other studies have reported that 21% of Parkinson's disease patients may carry a *GBA* mutation [7].

Genetic causes of Parkinson's disease

PARK loci	Gene	Chromosome	Form of Parkinson's disease	Origin
PARK1	*SNCA*	4q21	AD	Greece and Italy
PARK2	*PARK2* (parkin)	6q25.2–q27	AR J	Japan
PARK3	Unknown	2p13	AD	Europe
PARK4	*SNCA*	4q21	AD	Iowa
PARK5	*UCHL1*	4p14	AD and idiopathic	Germany
PARK6	*PINK1*	1p35–p36	AR	Italy
PARK7	*PARK7 (DJ1)*	1p36	AR and EO	Europe
PARK8	*LRRK2*	12q12	AD and idiopathic	Japan
PARK9	*ATP13A2*	1p36	Kufor–Rakeb syndrome and EO Parkinson's disease	Jordan, Italy, and Brazil
PARK10	Unknown	1p32	Idiopathic	Iceland
PARK11	*GIGYF2*	2q36–q37	AD and idiopathic	North America
PARK12	Unknown	X	Familial	North America
PARK13	*HTRA2*	2p13	Idiopathic	Germany

Figure 1.2 Genetic causes of Parkinson's disease. AD, autosomal dominant; AR, autosomal recessive; EO, early onset; J, juvenile.