Atypical Parkinsonian Disorders
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Atypical Parkinsonian Disorders
Clinical and Research Aspects

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Series Editor’s Introduction

Since the original classic description of Parkinson’s disease, there have been swings in concept from a unitary disease with characteristic clinical features and unique neuropathologic changes to that of a more variable disorder with multiple etiologies owing to a spectrum of pathological processes. Originally, the terms paralysis agitans and Parkinson’s disease first used in the 19th century implied a unitary disease. The concept of parkinsonism as a special disease entity was supported by the stereotyped features of akinesia, rigidity, tremor, and postural instability. The appearance of postencephalic parkinsonism and later the recognition of “arteriosclerotic parkinsonism” led to the realization that there must be multiple forms of the disease. Idiopathic Parkinson’s disease finally became anchored by identification of the Lewy body, which provided the necessary objective marker for what, at least temporarily, quite remarkably came to be called “Lewy body disease.” However, the later discovery that parkinsonism and dementia arise from a more diffuse distribution of Lewy bodies led to the designation of dementia with Lewy bodies, one of the first of the new generation of atypical parkinsonian disorders to be recognized. Striatonigral degeneration, multiple system atrophy, progressive supranuclear palsy, and corticobasal degeneration soon followed and rapidly evolved from relatively exotic disorders to household words, at least among the rapidly growing community of movement disorder neurologists. Finally, more recently, even the unitary concept of idiopathic Parkinson’s disease has been shaken by the discovery of multiple genetic types of Parkinson’s disease that may occur with or without Lewy bodies.

Currently, patients are increasingly aware of the possibility of atypical parkinsonism. Many ask about it at early visits and understand their dismal prognosis and treatment prospects if they should have one of these disorders. Dr. Irene Litvan has been at the front line for many years in the effort to make sense of this bewildering array of atypical parkinsonian syndromes. In this volume she has brought together an impressive group of experts in the field. All aspects of these disorders are covered by highly knowledgeable and thoughtful investigators. Some of the clinical and scientific disciplines which are reviewed are clearly more mature than others, but it would be safe to say that our understanding of these disorders remains very much in its infancy. A particularly unique and very useful aspect of the book is that each chapter concludes with a section on future directions in research. As Dr. Litvan states in her preface, an important goal of this book is to enlist new researchers to further our knowledge about the cause and treatment of these devastating disorders. Atypical Parkinsonian Disorders: Clinical and Research Aspects will serve as the comprehensive reference to current state-of-the-art scientific developments in the field and will hopefully provide a launching pad for future fundamental discoveries in the pathophysiology and treatment of these currently hopeless disorders.

Daniel Tarsy, MD
The term “atypical parkinsonian disorders” has the unavoidable connotation of neurodegeneration. Neurodegeneration can be defined as a loss of neurons that is both selective (i.e., several neuronal systems are affected, but not all), and slow (although faster than similar effects caused by aging). This definition excludes both sequelae of brain insults and diffuse lesions of the nervous system such as vascular parkinsonism and encephalopathies (Chapter 23).

What’s in a name? A less depressing definition of parkinsonian disorders (or parkinsonism) might well be the following: an akinetic-rigid syndrome associated with the selective dysfunction of the nigrostriatal dopaminergic system. This definition is broad enough to include both typical and atypical neurodegenerative parkinsonian disorders. Parkinson’s disease is what we call a “typical” parkinsonian disorder. Parkinson’s disease is characterized by progressive akinesia and rigidity, usually unilateral at onset, with or without resting tremor, which responds significantly to levodopa treatment or other kinds of dopaminergic replacement therapy. However, the diagnosis of Parkinson’s disease is difficult to establish for several reasons:

1. Akinesia and rigidity are heterogeneous symptoms that can differ from one patient to another. Plastic rigidity (associated with the classical cogwheel phenomenon and predominant in the extremities), is different from the diffuse rigidity of the Gegenhalten type (rigidité oppositioniste) observed in atypical parkinsonian disorders. Akinesia is a general term that is frequently used inappropriately, and does in fact include several symptoms: akinesia per se, which means delayed initiation of movement (increased reaction time); bradykinesia (slowness of movement); hypokinesia (easily observed when testing repetitive movements of the extremities); difficulty in performing consecutive or sequential gestures; and decreased motivation to move, whatever its origin.

2. Parkinson’s disease is also difficult to diagnose because in most patients, other symptoms occur during the course of the disease, including cognitive decline (cortical and/or subcortical dysfunction) and axial symptoms such as dysarthria, swallowing difficulties, neck rigidity, postural abnormalities, urinary dysfunction, gait disorders, postural instability (all symptoms that represent a major component of atypical parkinsonian disorders), which respond poorly to Levodopa replacement therapy.

3. Before reaching a diagnosis of Parkinson’s disease, it is indeed crucial to be sure that the patient shows a significant response to levodopa treatment (or related therapy) used at adequate doses. What we mean by “significant” is either (a) an objective 30% improvement in parkinsonian motor disability (as evaluated before and after the administration of Levodopa), or (b) a subjective 30% improvement in motor disability as assessed from the patient interview, either at the start of treatment (i.e., “What was the percentage improvement in your condition when you received levodopa treatment for the first time?”) or later, during the course of the disease (i.e., “What was the percentage improvement in your condition when you took your first dose of levodopa?”). A clear-cut response to levodopa treatment (or dopamine agonists) is a prerequisite for a diagnosis of Parkinson’s disease, as it indirectly reflects the existence of a dysfunction of dopaminergic neurons in the striatum of patients. A lack of response to levodopa treatment (using adequate doses of levodopa) does not mean that there is no nigrostriatal deficiency (inherent in the definition of parkinsonism), but rather indicates that the reestablishment of normal brain dopaminergic transmission is not followed by an improvement in motor disability owing to the presence of nondopaminergic lesions located downstream of the output of the basal ganglia.

4. Finally, Parkinson’s disease is a heterogeneous disorder that includes several clinical phenotypes identified in recent years. The term “Parkinson’s disease” should in fact be replaced by “Parkinson’s diseases,” as several phenotypes of this disorder have been described resulting from
different mutations within different genes in patients with familial and sporadic forms of the disease. This suggests that many, if not all, clinical phenotypes of sporadic Parkinson’s disease have either a monogenic cause or at least involve a significant predisposition to develop the illness.

By deduction, atypical parkinsonian disorders can be defined as a mirror image of typical parkinsonism, i.e., an akinetic-rigid syndrome that is not improved by the reestablishment of normal dopaminergic transmission in the brain. Within the spectrum of diseases that constitute the syndrome of atypical parkinsonism, akinesia, and rigidity become rapidly severe and characteristically involve the axis of the body. Shortly after onset other signs become more prominent, leaving parkinsonism in the background: supranuclear gaze palsy, early falls and frontal lobe symptomatology will suggest progressive supranuclear palsy (Chapter 18); dysautonomia and cerebellar signs: multiple system atrophy (Chapter 20); unilateral apraxia, corticobasal degeneration (Chapters 13 and 19); dementia of the cortico-subcortical type with early visual hallucinations, Lewy body disease (Chapter 21). Additional symptoms may help to establish the diagnosis of atypical parkinsonism, including speech disorders (Chapter 14), various behavioral disorders (Chapters 12 and 13), dystonia, pyramidal signs and pseudo-bulbar palsy. A thorough physical examination (Chapter 10) will either allow a final diagnosis to be made or will suggest appropriate laboratory tests. Apart from electrophysiological investigations (Chapter 28), which are mostly interesting in terms of research, three investigations will provide decisive information as far as the diagnosis is concerned: a careful neuropsychological examination to evaluate the different cortical (and subcortical) components of cognitive disorders (Chapters 13, 16, and 24), ocular movement recording (Chapter 17), and neuroimaging, with particular reference to MRI (Chapter 25) (functional neuroimaging and positron emission tomography are mainly used for research purposes). Nevertheless, the diagnosis of atypical parkinsonian disorders is not easy to establish, and proves to be erroneous in about 10% of cases even in the hands of experts in the field of movement disorders.

The best definition of atypical parkinsonism is probably an anatomo-clinical one, since postmortem examination of the brains of patients does not always result in an accurate histological diagnosis. There is, indeed, an increasing number of postmortem cases in which histopathology does not entirely fulfill the diagnostic criteria for these disorders (Chapters 4 and 8), either because the distribution of the lesions is unusual or because atypical histopathological stigmata are associated with the characteristic hallmarks of the different diseases. Histopathological phenotypes have recently been identified, based on the presence of various abnormal tau proteins (Chapter 5) or synucleins (Chapter 6). These pathological classifications are of great interest in studying the pathogenesis of the disorders but, unfortunately, are of limited value to the patients and their caregivers. It is hoped that molecular and cellular research in these fields will help to delineate new clinical and pathological entities alongside those that have currently been identified in clinical practice.

During the past 5 years, aided by the unrelenting efforts of disease associations and lay groups, an enormous amount of research has been undertaken with two main aims. One is to find new symptomatic treatments. This implies understanding the neuronal substrate underlying each of the many and complex symptoms characteristic of each disorder, with a special focus on the anatomo-physiological organization of the neocortex and basal ganglia. The other is to cure the diseases, i.e., to understand the various mechanisms of nerve cell death that are directly related to the cause (or causes) of the diseases. The only way to define a disease is, indeed, to define it by its origin, whether the cause is genetic-monofactorial inheritance or multifactorial predisposition (Chapter 9), whether environmental factors play a predominant or contributive role (Chapter 3), or whether both of these causes are involved. The progress of research into the pathophysiology and pathogenesis of all these disorders is impressive, when one takes into account their relative recent description (Chapter 2).

An effort needs to be made by our institutions to develop research programs specifically dedicated to atypical parkinsonian disorders, from molecular and cellular biology to neurophysiology and behavioral sciences. The main objective, during the years ahead, must be to discover new drugs to
improve the symptoms, to limit or stop the process of cell loss, and to repair the affected brain tissues. Yet, there has been a notable improvement in patient management during the last few years (Chapter 11). Though there is no available curative treatment (does one know of a neurodegenerative disease that can be cured?), there are numerous symptomatic treatments (Chapter 20) and rehabilitation approaches (Chapter 30) that will help to reduce disability and improve both the patients’ well being and the quality of life for both patients and caregivers. This is perhaps the most important message of this book, *Atypical Parkinsonian Disorders: Clinical and Research Aspects*.

Irene Litvan, who has devoted the greater part of her clinical and research activities to these mysterious and distressing disorders, is to be applauded for having convinced so many leading experts in the field to contribute to this promising book.

*Yves Agid, MD, PhD*
The “atypical parkinsonian disorders,” previously known as “Parkinson plus syndromes,” are characterized by a rapidly evolving parkinsonism that usually has a poor or transient response to dopaminergic therapy and often associates with one or more atypical features. These disorders may be difficult to accurately diagnose, but an early and correct diagnosis is relevant for both patients and physicians, since it allows for appropriate management and prognosis, which in turn, improves patients and families quality of life. An accurate diagnosis also allows patients to participate in research and may increase survival.

This book, Atypical Parkinsonian Disorders: Clinical and Research Aspects, the first of its kind, provides an all-encompassing view of the current status of atypical parkinsonian disorders from both clinical and research viewpoints. Its goals are threefold: (1) to provide critical, state-of-the-art insight into both the clinical and research aspects of the atypical parkinsonian disorders; (2) to increase clinicians’ index of suspicion by providing them with appropriate tools for an accurate diagnosis; and (3) to enlist new researchers who will further our knowledge on the etiopathogenesis of these devastating disorders and hopefully allow for the identification of new therapeutic paradigms.

The chapters have been written by world-leading experts in their fields, and their efforts have culminated in a truly unique compilation of what is currently known about the historic aspects, epidemiology, neuropathology, genetics, neuropsychological, neuropsychiatric, ophthalmologic, neurologic, and radiologic diagnostic evaluations and therapeutic approaches, as well as overall understanding of atypical parkinsonian disorders. We anticipate that the enclosed DVD, containing visual and auditory aids, will help clinicians, fellows, residents, students, and neuroscience researchers alike to characterize and differentiate the various atypical parkinsonian disorders. Audio segments will be helpful to characterize and distinguish the diverse speech disturbances found in these disorders. Current controversies and the role of genetics and neurological and pathological phenotypes in the nosologic classification of these disorders as well as each chapter author’s view on where research should focus in the future are offered.

Movement disorder specialists, neurologists, neuro-ophthalmologists, neuropathologists, psychiatrists, neuropsychologists, geriatricians, and physical and occupational therapists alike may find these pages indispensable. Clinicians, residents, and students may find the chapters on epidemiology, medical and physical history techniques, neuropsychiatric and neuropsychological testing, praxis, visuospatial cognition, neuro-ophthalmology, and speech and language assessments invaluable tools for clinical diagnosis, while the disease-specific videos, tables, and figures may provide them with a visual handbook for frequent reference. Researchers and fellows will gain further insight into their own work, which will add to the progression of the knowledge presented in these pages.

Atypical Parkinsonian Disorders would have not been possible without the hard work and dedication of friends and colleagues who graciously provided state-of-the-art chapters, excellent figures, and unique video and audio segments that we believe are crucial tools for learning, teaching, and research. I want particularly to thank Dr. Daniel Tarsy for encouraging me to edit this exciting book. I also want to acknowledge the help provided by Theresa Perry and Whitney Rogers in its preparation, and the support from Michael Gruenthal and the University of Louisville. Finally, I want to thank patients and caregivers for their time and dedication to our research and for their patience waiting for a therapeutic paradigm shift. It is hoped that their increasing participation in research and the knowledge summarized in this book will provide the needed enthusiasm to attract new researchers into this field who will further our understanding of these diseases so they can soon be eradicated from the face of the earth.

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Carol Frattali, co-author of Chapter 16 on speech and language, passed away suddenly while this book was in press. Carol was a superb clinician, valued colleague, and was developing a new program of research at the National Institutes of Health when she was taken from us. Carol was not afraid to begin a new research project, no matter how difficult the challenge. I am sure that attitude kept her young at heart and permeated all facets of her life. She was inspirational to patients, colleagues and friends, and we all surely miss her.

Irene Litvan, MD
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To use this DVD-ROM, you will need a computer with a DVD drive. This DVD will not operate in a CD-ROM drive. To view the PDF files on this DVD-ROM, you will need Adobe Reader. To view the video clips, you will need an MPEG-1 compatible video player (Windows Media Player, Quicktime, Real Player, etc.). Most computers and operating systems will play these videos without further installation or modification.
1

What is an Atypical Parkinsonian Disorder?

Irene Litvan

INTRODUCTION

A parkinsonism is a syndrome defined by akinesia associated with rigidity or rest tremor. The akinesia can be expressed as motor slowness (bradykinesia) or as a paucity of movement (hypokinesia), i.e., difficulty in the initiation of or decreased amplitude of movements such as arm swing or facial expression. This syndrome is usually the result of a dysfunctional nigrostriatal pallidal pathway. Impairment of postural reflexes is not included as one of the features of the parkinsonian syndrome since abnormal postural reflexes are generally the consequence of dysfunction of other motor pathways. There are a variety of causes of parkinsonism, but Parkinson’s disease (PD) is the most common (Fig. 1). Although there is extensive literature on PD, this is one of the few books dedicated to the remaining atypical parkinsonian disorders. To appropriately diagnose PD, one should be aware of when to suspect that a patient does not have PD and may be suffering from one of these atypical disorders.

The “atypical parkinsonian disorders” (previously known as “Parkinson plus syndromes”) are characterized by a rapidly evolving parkinsonism that has a poor or transient response to dopaminergic therapy and often associates with one or more atypical features for PD. Some of these features include early presence of postural instability, early autonomic failure, vertical supranuclear gaze palsy, pyramidal or cerebellar signs, alien limb syndrome, and apraxia (Table 1; see corresponding video segments on accompanying DVD). Making the distinction between these two major groups of disorders is critical for both clinical practice and research because the prognosis and treatment of patients with an atypical parkinsonian disorder and those with PD differ (1–4). In the clinical setting, although patients with PD may have an almost normal life-span if treated appropriately (4–6), those with atypical parkinsonian disorders have a shorter survival time and more complications occur at early stages and are frequently more severe (3,7–10) (see Table 2 for an example). Moreover, indicated therapies (particularly surgical approaches) differ significantly since some may not be indicated to treat patients with atypical parkinsonian disorders. Until recently, clinicians would “lump” all the atypical parkinsonian disorders together and would only distinguish between this group and PD. However, the need for early identification of the different atypical parkinsonian disorders is becoming increasingly recognized (11), as their prognosis, complications, and survival differ (3,7,8,12–19).

For research, this distinction is crucial; homogenous groups are a necessity for studies that lead to firm conclusions. Genetic, analytical, epidemiological, and clinical trials require the inclusion of accurately diagnosed patients. However, diagnosis of the atypical parkinsonian disorders can be at times challenging (20–25) since these disorders may have similar presentations at early disease stages.
Fig. 1. PSP, progressive supranuclear palsy; CBD, corticobasal degeneration; MSA, multiple system atrophy; DLB, dementia with Lewy bodies; FTDP-17, frontotemporal dementia with parkinsonism linked to chromosome 17; SCAs, spinocerebellar atrophy; NBIA, Neurodegeneration With Brain Iron Accumulation, previously called Hallervorden–Spatz Syndrome; HIV, human immunodeficiency virus.

Table 1
When Should an Atypical Parkinsonian Disorder be Suspected?

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<th>Features suggestive of an atypical parkinsonian disorder</th>
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<td><strong>Motor</strong></td>
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<tr>
<td>Rapid disease progression</td>
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<td>Early instability and falls</td>
</tr>
<tr>
<td>Absent, poor, or not maintained response to levodopa therapy</td>
</tr>
<tr>
<td>Myoclonus</td>
</tr>
<tr>
<td>Pyramidal signs</td>
</tr>
<tr>
<td>Cerebellar signs</td>
</tr>
<tr>
<td>Early dysarthria and/or dysphagia</td>
</tr>
<tr>
<td>Early dystonia/contractures (unrelated to treatment)</td>
</tr>
<tr>
<td><strong>Autonomic Features</strong></td>
</tr>
<tr>
<td>Impotence/decreased genital sensitivity in females</td>
</tr>
<tr>
<td>Early orthostatic hypotension unrelated to treatment</td>
</tr>
<tr>
<td>Early and/or severe urinary disturbances</td>
</tr>
<tr>
<td><strong>Oculomotor</strong></td>
</tr>
<tr>
<td>Marked slowing of saccades</td>
</tr>
<tr>
<td>Difficulty initiating saccades, gaze (oculomotor apraxia)</td>
</tr>
<tr>
<td>Supranuclear gaze palsy</td>
</tr>
<tr>
<td>Nystagmus</td>
</tr>
<tr>
<td><strong>Cognitive and behavioral</strong></td>
</tr>
<tr>
<td>Early and severe frontal or cortical dementia</td>
</tr>
<tr>
<td>Visual hallucinations not induced by treatment</td>
</tr>
<tr>
<td>Ideomotor apraxia</td>
</tr>
<tr>
<td>Sensory or visual neglect/cortical disturbances</td>
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Table 2

Progression of Various Parkinsonian Disorders

<table>
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<tr>
<th>Disorder</th>
<th>Sample Size (N)</th>
<th>Median Age at Onset (yr)</th>
<th>Median HY II Latencies (mo)</th>
<th>Median HY III Latencies (mo)</th>
<th>Median HY IV Latencies (mo)</th>
<th>Median HY V Latencies (mo)</th>
<th>Median survival After HY V Onset (mo)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PD</td>
<td>18</td>
<td>60</td>
<td>36*</td>
<td>66**</td>
<td>166**</td>
<td>179**</td>
<td>12</td>
</tr>
<tr>
<td>CBD</td>
<td>13</td>
<td>64</td>
<td>25</td>
<td>42</td>
<td>55</td>
<td>62</td>
<td>43</td>
</tr>
<tr>
<td>DLB</td>
<td>11</td>
<td>65</td>
<td>12</td>
<td>43</td>
<td>45</td>
<td>59</td>
<td>12</td>
</tr>
<tr>
<td>MSA</td>
<td>15</td>
<td>56</td>
<td>0</td>
<td>3</td>
<td>38</td>
<td>56</td>
<td>9</td>
</tr>
<tr>
<td>PSP</td>
<td>24</td>
<td>65</td>
<td>—</td>
<td>0</td>
<td>38</td>
<td>56</td>
<td>9</td>
</tr>
</tbody>
</table>

Modified from Muller et al., with permission (17).

*p < 0.05; **p < 0.001 Parkinson’s disease (PD) vs atypical parkinsonian disorders (CBD, DLB, MSA, PSP), (Mann–Whitney U Test). PD patients had a significantly longer latency to each Hoehn and Yahr (HY) stage than those with atypical parkinsonian disorders, confirming the more rapid progression of motor disability in patients with atypical parkinsonian disorders. Most MSA and PSP patients developed postural instability with or without falls significantly earlier than those with CBD and DLB. Postural instability and falls are the most common initial symptoms in PSP, and almost all PSP patients developed an HY stage III within 1 yr of motor onset. The majority of MSA (67%), the majority of DLB (55%), and 38% of CBD patients also reached this stage early.

(i.e., progressive falls, parkinsonism not responsive to dopaminergic therapy). Tell-tale signs may take 2 to 4 yr after symptom onset to develop, or early features may be either disregarded or misdiagnosed by clinicians.

Misdiagnosis of these disorders is frequent, as patients exhibit a variety of symptoms that may lead them to be initially evaluated by internists or specialists (e.g., ophthalmologists, urologists, neurologists, psychiatrists, neurosurgeons). For example, it is not unusual for a patient with progressive supranuclear palsy (PSP) to be evaluated by several ophthalmologists (and have their glasses changed several times) or to have multiple unnecessary studies for evaluating the cause of their falls prior to being seen by a neurologist. Similarly, patients with corticobasal degeneration (CBD) may present after unsuccessful carpal tunnel surgery, or those with multiple system atrophy (MSA) may present only after failed prostate surgery; in both cases these types of surgery can worsen the patients’ symptoms. Diagnostic accuracy would greatly improve, however, if clinicians from different disciplines would have a broader knowledge of the typical and atypical presentations of these disorders and use proposed clinical diagnostic criteria (26).

In the absence of biological markers and known pathogenesis, current diagnosis requires the presence of certain clinical features that allow for clinical diagnosis and eventual pathologic verification. As a result, diagnostic accuracy requires that both clinical and pathological sets of diagnostic criteria be valid and reliable (27,28). Neuropathologic diagnostic criteria for most parkinsonian disorders have been validated and standardized (27,29); the exceptions are those for dementia with Lewy bodies (DLB) and PD with later onset dementia (PDD). Similarly, recently the clinical diagnostic criteria have undergone the same process of rigorous operationalization and validation for most of these disorders (26,30–35).

Though consensus for the diagnosis of several of these disorders has been put forward (30–33), and validation studies of diagnostic criteria have been performed for most of the atypical parkinsonian disorders (36), refinement of the criteria is still needed (36). In practice, clinicians are exposed to patients who exhibit different parkinsonian disorders, and so validation studies should compare the accuracy of several sets of criteria with neuropathology. The Scientific Issue Committee of the Movement Disorder Society created a task force to critically review the accuracy of different sets of diagnostic criteria for parkinsonian disorders (36). The task force analyzed how well each set of diagnostic criteria identified all subjects with the disease as having the disease (i.e., sensitivity); identified sub-
Table 3
Validity of the Clinical Diagnostic Criteria for PSP, MSA, DLB, and VaD

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Criteria</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Author</th>
<th>n/n TOTAL</th>
</tr>
</thead>
<tbody>
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<td>PSP</td>
<td>Blin et al. (47)</td>
<td>21/63</td>
<td>100/85</td>
<td>100/63</td>
<td>Litvan et al. (29)</td>
<td>24/83</td>
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<tr>
<td></td>
<td>Probable/Possible</td>
<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>Blin et al. (47)</td>
<td>13/34</td>
<td>100/98</td>
<td>100/85</td>
<td>Litvan (19)</td>
<td>24/105</td>
</tr>
<tr>
<td></td>
<td>Probable/Possible-1st visit</td>
<td>55/89</td>
<td>94/74</td>
<td>73/50</td>
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<td></td>
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<tr>
<td></td>
<td>First visit</td>
<td>72</td>
<td>93</td>
<td>76</td>
<td>Litvan et al. (19)</td>
<td>24/105</td>
</tr>
<tr>
<td></td>
<td>Last visit</td>
<td>80</td>
<td>92</td>
<td>76</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Collins et al. (51)</td>
<td>25/42</td>
<td>100/92</td>
<td>100/67</td>
<td>Litvan et al. (29)</td>
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<td>First visit</td>
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<td>94</td>
<td>76</td>
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<td>92</td>
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<td>95</td>
<td>77</td>
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<tr>
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<td>87</td>
<td>65</td>
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<td></td>
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<td>58</td>
<td>95</td>
<td>82</td>
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<td>NINDS-SPSP</td>
<td>50/83</td>
<td>100/93</td>
<td>100/83</td>
<td>Litvan et al. (29)</td>
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<td>100/96</td>
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<td>80</td>
<td>Hughes (52)*</td>
<td>20/143</td>
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<tr>
<td></td>
<td>Tolosa et al. (50)</td>
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<td>Litvan et al. (21)</td>
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<tr>
<td></td>
<td>First visit</td>
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<td>Last visit</td>
<td>69</td>
<td>97</td>
<td>80</td>
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<td>MSA</td>
<td>Clinician’s prospective diagnosis in life</td>
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<tr>
<td></td>
<td>First visit</td>
<td>22</td>
<td>92</td>
<td>86</td>
<td>Oaski et al. (33)</td>
<td>51/59</td>
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<tr>
<td></td>
<td>Last visit</td>
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<td>86</td>
<td>86</td>
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<td>Consensus Criteria (55)</td>
<td>16/28</td>
<td>100/93</td>
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<td>Hughes et al. (52)*</td>
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<td>95/82</td>
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<td>87/86</td>
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</table>

(continued)
Table 3 (continued)

Validity of the Clinical Diagnostic Criteria for PSP, MSA, DLB, and VaD

<table>
<thead>
<tr>
<th>Disorder</th>
<th>Criteria</th>
<th>Sensitivity (%)</th>
<th>Specificity (%)</th>
<th>Positive Predictive Value (%)</th>
<th>Author</th>
<th>n/n TOTAL</th>
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<td>Quinn (54)</td>
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<td>97/79</td>
<td>68/30</td>
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<td>16/105</td>
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<td>50</td>
<td>100</td>
<td>Mega (56)</td>
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<td>75</td>
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<td>NR</td>
<td>55.8</td>
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<td>100</td>
<td>100</td>
<td>Holmes (57)</td>
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<td>84/23</td>
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<td>100/94</td>
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<td>95/91</td>
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<td>8/0</td>
<td>83/NA</td>
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<td>100</td>
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<td>75</td>
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<td>14/105</td>
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<td>28.6</td>
<td>99</td>
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<td>Litvan (61)</td>
<td>14/105</td>
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<td>99.6</td>
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<td>VaD</td>
<td>Queen Square movement disorder neurologists’ diagnosis</td>
<td>25</td>
<td>98.6</td>
<td>33.3</td>
<td>Hughes et al. (52)*</td>
<td>3/143</td>
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</tbody>
</table>

Revised from Litvan et al. (36).

*Prospective studies. Note that all other studies are retrospective. CDLB, consensus criteria for dementia with Lewy bodies.

Classifiers without the disease as not having the disease (i.e., specificity); and provided reasonable estimates of disease risk (i.e., positive predictive value or PPV). See summary table (Table 3) and refer to the actual publication (36) and specific disease-related chapters in this book for detailed comments. Overall, most of these criteria are specific but not very sensitive. It is worth noting that a validation of pathologic and clinical diagnostic criteria for PD is still needed. Standardization of diagnostic criteria, clinical scales, and identification of outcome measures (37,38) set the stage for conducting appropriate clinical trials.

CLASSIFICATION OF ATYPICAL PARKINSONIAN DISORDERS

Atypical parkinsonian disorders can be caused by primary or secondary diseases (see Fig. 1). The primary causes consist of neurodegenerative processes such as PSP, CBD, MSA, DLB, and PDD. Interestingly, one of the earlier historical cases thought to have the typical features of PSP was recently found to have a midbrain tumor through autopsy examination. As discussed in Chapter 23, secondary causes also include drugs, infections, toxins, or vascular disease (21,23,39–44).
An alternative classification (mostly helpful for research and future therapeutic approaches rather than for clinical use) considers the type of aggregated proteins in the brain lesions and classifies these disorders as tauopathies and synucleinopathies (Table 4; see also Chapters 4 and 8). Commonalities in clinical, biological, or genetic findings question the nosological classification of some of these disorders; for further information the reader is referred to Chapters 8 and 9.

PSP and DLB/PDD are the most frequent neurodegenerative primary cause of an atypical parkinsonian disorders (31,45–47). A good history and physical examination will rule out drug-induced atypical parkinsonian disorders and supports the diagnosis of these specific disorders (Chapter 10). Each disorder is specifically covered in Chapters 18–23. The role of ancillary and laboratory tools to assist in the diagnosis of these disorders is discussed in Chapters 11–16 and 24–27. Ancillary tests (e.g., neuroradiologic or cerebrospinal studies) also help with the diagnosis of disorders caused by vascular diseases, tumors, or infection (e.g., Whipple’s disease, Creutzfeldt–Jakob disease, human immunodeficiency virus). Specific therapeutic and rehabilitation approaches for all of these disorders are provided in each disease chapter and an overview of future biologic and rehabilitation approaches is provided in Chapters 28 and 29.

It is our expectation that this book will continue to improve the accuracy of the diagnosis of these disorders by raising awareness of their different presentations and by increasing diagnosticians’ index of suspicion. An early and accurate diagnosis will allow better management of these patients and increase research potential.

There has been a tremendous increase in our knowledge concerning the proteins that characterize and aggregate in the brain in each of these disorders. Moreover, animal models are now available to help test potential new therapies (see Chapters 5 and 6). Hence, in addition to serving as a reference source, it is hoped that this book will stimulate new investigators to join us in the search for answers to the multiple questions raised throughout the book and in the battle against these disorders. It is anticipated that a better understanding of these diseases, their nosology, and etiopathogenesis (see Chapters 3–9) will lead to better management, quality of life (see Chapter 17), and treatment for patients who suffer them. We anticipate that the eradication of these devastating diseases from the face of the earth will occur in not such a remote future.

**LEGEND TO VIDEOTAPE**

Postural Instability: Video segment shows a patient with a history of falls and an impaired postural reflex with the backward pull test. The patient would have fallen, unless aided by the examiner. The gait is stable but slightly wide-based.

Supranuclear gaze palsy: This patient shows a severe limitation in the range of ocular motor movements observed, which affects more upward than downward voluntary and pursuit gaze. As observed, the oculocephalic reflex is preserved when the the doll’s head maneuver is performed.

Slowing of vertical saccades: Patient shows markedly slow vertical saccades and relatively preserved horizontal saccades.
Ocular motor apraxia: The patient shows difficulty initiating the voluntary gaze and saccades but exhibits a preserved pursuit and optokinetic nystagmus. Once the saccades are initiated their speed is normal.

Corticosensory deficits: This patient shows right sensory neglect and agraphesthesia. These lateralized cognitive features in conjunction with the progressive development of a right ideomotor apraxia, dystonia, and stimulus sensitive myoclonus led to the diagnosis of corticobasal degeneration (corticobasal syndrome).

Limb kinetic apraxia: The performance of this patient does not improve with imitation. Movements are coarse and do not represent the intended action.

Blepharospasm: Difficulty opening the eyes because of inhibition of eyelid opening, which is followed by blepharospasm.

REFERENCES

Classification

Studying archetypes is a fundamental task in nosography. Duchenne de Boulogne practiced it instinctively, and many others have done it before and after him: It is indispensable, and the only way to extract a specific pathological state from the chaos of imprecision. The history of medicine, which is long and grand, shows this truth well. But once the archetype is established, the second nosographic operation begins: dissect the archetype and analyze its parts. One must, in other words, learn how to recognize the imperfect cases, the *formes frustes*, or examples where only one feature occurs in isolation. Using this second method, the physician will see the archetypal illness in an entirely new light. One’s scope enlarges, and the illness becomes much more important in the doctor’s daily practice. To the patient’s benefit, the doctor becomes attentive and sensitive to recognizing a disease, even when it is in its earliest developmental stages (1).

**INTRODUCTION**

As shown in the above quotation from Jean-Martin Charcot’s teaching of the late 19th century, the concept of *atypical Parkinsonian disorders* and *formes frustes* of the classic disease emerged in parallel with the definition of Parkinson’s disease itself. In 1817, James Parkinson, a London general practitioner, described resting tremor and gait impairment in the small sample of subjects whose symptoms would later be coalesced into a disorder that would bear his name (2). Nearly 50 yr later, Charcot returned to this early description and used his large patient population to study Parkinson’s disease in full detail. With access to thousands of elderly patients who lived in the sprawling hospital-city of the Hôpital de la Salpêtrière in central Paris, Charcot studied the evolution of signs from very early disease through the most advanced stages (3,4). Charcot used specialized recording equipment to distinguish the rest tremor of typical Parkinson’s disease from the tremors typical of multiple sclerosis and other conditions where posture- or action-induced exacerbation occurred (5). He was particularly adept in distinguishing bradykinesia as a cardinal feature of the illness and separating it from weakness. These studies led him to discourage the original designation of *paralysis agitans*, because patients did not develop clinically significant loss of muscle power until very late. Charcot further emphasized the distinctive elements of rigidity and delineated its distinction from spasticity or other forms of hypertonicity. Finally, he succinctly described the stance and gait of the subject with Parkinson’s disease:

His head bends forward, he takes a few steps and they become quicker and quicker to the point that he can even bump into the wall and hurt himself. If I pull on his trousers from behind, he will retropulse in the same distinctive way (4).
Charcot’s celebrated teaching courses and publications established these four features—rest tremor, bradykinesia, rigidity, and postural reflex impairment in balance and stance—as the cardinal features of typical Parkinson’s disease. Charcot complemented these studies with documentation of trophic and arthritic features of the illness, with further studies of pain and autonomic nervous system alterations, and with pharmacological observations (3). At the same time, however, as indicated in the introductory quotation of this chapter, he emphasized the importance of recognizing cases that he termed variants or formes frustes, cases that were similar to and yet distinct from the classic, archetypal form of the disease. These cases were termed atypical Parkinson’s disease, at a time when the pathological substrate of Parkinson’s disease itself remained unknown. As a historical introduction to the conditions that are the primary focus of this book and today collectively termed atypical parkinsonian disorders, these historical cases provide source material for the early study of conditions later to be separated from Parkinson’s disease and defined in the mid- and late-20th century as progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration.

EARLY CONCEPTS OF ATYPICAL PARKINSON’S DISEASE

Nineteenth-century neurologists recognized three basic categories of parkinsonism that were suitably different from typical Parkinson’s disease to merit designation: cases without typical tremor, those with atypical postures (extension rather than flexion), and those with marked asymmetry in the form of seeming hemiplegia. Within these categories, modern neurologists will find characteristics that typify progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration, though these latter diagnoses were not defined specifically until clinical-pathological studies distinguished them as distinct from Parkinson’s disease itself. Each of these clinical categories is described from the perspective of 19th-century neurology and then followed by a specific discussion of the history of progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration.

Parkinsonism Without Prominent Rest Tremor

Early neurologists recognized resting tremor as the most distinctive feature of typical Parkinson’s disease, and placed patients who had unusual, intermittent tremor patterns or no tremor into the clinical category termed “Parkinson’s disease without tremor” (3,4). Some of these cases actually had tremor, but the movements were mild in severity or intermittent and primarily induced with emotion or action (3). It is possible that myoclonus, a feature frequently seen in corticobasal degeneration, and mild action tremor that can be seen in multiple system atrophy would have been categorized as one of these intermittent tremors. Myoclonus was appreciated in the 19th century, especially by Germanic and Austrian researchers (6,7), but not specifically designated as an aspect of atypical Parkinson’s disease. Charcot studied tremor extensively and drew attention to its typical features in Parkinson’s disease. He conducted his tremor examination with patients at rest and during activity. In addition to clinical observation, he used tremor oscillometers (Fig. 1) and small portable lamps that he attached to the shaking extremities in order to record the trajectory movements on light-sensitive paper (8). To accentuate an appreciation of very mild tremor, he attached feathers or other lightweight objects to the shaking body part to magnify the oscillations. He held strongly that titubation was not part of typical Parkinson’s disease, but lip and tongue tremors could occur. Because parkinsonian cases without tremor were still considered as variants of the primary disease, Charcot advocated the use of the term Parkinson’s disease, rather than “paralysis agitans,” as coined by Parkinson himself (3,4).

Parkinsonism With Atypical Postures

Charcot studied muscle tone extensively and established that most Parkinson’s disease subjects showed a flexed posture with the shoulders hunched forward, neck bent down toward the chest, and the arms held in partial flexion at rest. In contrast, he found a small number of parkinsonian patients
who were bradykinetic, unstable in their stance and gait, and yet showed a very different posture. These subjects, collectively termed “Parkinson’s disease with extended posture,” were of particular interest to Charcot, and he recognized several features of these cases that distinguished them from the archetypal cases of Parkinson’s disease. These cases are further discussed later in the subheading on Progressive Supranuclear Palsy and shared several additional features of this diagnosis including the distinctive facial expression, swallowing difficulties, and frequent falls (Fig. 2).

**Hemiplegic Parkinson’s Disease**

Early neurologists considered Parkinson’s disease to be a bilateral condition, but often commented on the mild asymmetry of tremor, especially in the early years of disease. Within the context of this asymmetric but bilateral archetype, they distinguished another form of Parkinson’s disease that was highly asymmetric with prominent disability in the involved upper extremity beyond that expected with bradykinesia alone (3). Collectively termed *hemiplegic Parkinson’s disease*, these cases form a large series in the French neurological literature of the late 19th century and include cases of abrupt strokelike onset as well as slowly progressive disability (9) (Fig. 3). They are discussed in the section on corticobasal degeneration, because they clinically fit best into this designation among the group of atypical parkinsonian disorders. Because infectious disease (abscess and hemorrhagic strokes especially from military tuberculosis) were frequent disorders in the 19th century, some of these cases may not have related to primary neurodegeneration. Furthermore, autopsy reports were not systematically recorded, so that analysis of cases as corticobasal degeneration remains only suggestive.

Fig. 1. Tremor recording machine used by Charcot to separate cases of typical rest tremor from those with postural tremor and action-induced tremor. Early studies focused on the differentiation by tremor type of multiple sclerosis and Parkinson’s disease, but this apparatus was later used to study the various *formes frustes* of Parkinson’s disease as well. In the insert, tremor recordings are shown for resting posture (AB) and action (BC) in patients with different tremor patterns. From *Dictionnaire Encyclopédique des Sciences Médicales*, 1883.
Fig. 2. Drawing by J-M Charcot comparing two patients: (left) typical Parkinson’s disease with flexed posture and (right) another patient with an atypical variant of extended posture (4).

Fig. 3. Photograph from an article by Dutil (17) showing asymmetric parkinsonism suggestive of corticobasal degeneration but with an extended trunk and neck posture with gaze impairment suggestive of progressive supranuclear palsy.
HISTORICAL DESCRIPTIONS OF ATYPICAL PARKINSONIAN DISORDERS

Progressive Supranuclear Palsy

In 1963, Steele, Richardson, and Olszewski presented a report at the American Neurological Association of a new syndrome typified by parkinsonism, marked vertical gaze paresis, dementia, and axial rigidity \( (10,11) \). Though they felt they were describing a new syndrome, they referred colleagues to similar cases from the recent past \( (12–14) \) (Fig. 4). H. Houston Merritt opened the discussion, commenting that he had not seen similar cases, that the involved areas all related to cell populations of similar phylogenetic age, and that dementia was of particular interest. F. McNaughton acclaimed: “I believe that the authors have described a clear-cut neurological syndrome and to judge from the pathological studies, it may, in fact, represent a new disease entity.” D. Denny-Brown was less sure and ascribed the cases to variants of Jakob’s “spastic pseudosclerosis” \( (10) \).

Prior to these 20th-century descriptions, several cases of “Parkinson’s disease with extended posture” can be identified with characteristics suggestive of progressive supranuclear palsy. Charcot presented a man, named Bachère, to his students on several occasions (see Fig. 2). Commenting on June 12, 1888, Charcot mentioned that Bachère did not have marked tremor and emphasized the issue of extension posture:

There is something else unusual here worth noting. Look how he stands. I present him in profile so you can see the inclination of the head and trunk, well described by Parkinson. All this is typical. What is atypical, however, is that Bachère’s forearms and legs are extended, making the extremities like rigid bars, whereas in the ordinary case, the same body parts are partly flexed. One can say then that in the typical case of Parkinson’s disease, flexion is the predominant feature, whereas here, extension predominates and accounts for this unusual presentation. The difference is even more evident when the patient walks \( (3) \).

In addition to extended posture, this patient had particular facial bradykinesia and contracted forehead muscles \( (15) \). Charcot commented that the patient had the perpetual look of surprise because the eyes remained widely opened and the forehead continually wrinkled (Fig. 5). In a modern setting, Jankovic has detailed similar facial morphology in Parkinsonism-plus patients, specifically those with progressive supranuclear palsy \( (16) \). The extended truncal posture of this patient would be compatible with the posture of progressive supranuclear palsy, although Charcot did not comment on specific supranuclear eye movement abnormalities. Another Salpêtrière patient with “Parkinson’s disease in extension” was described by Dutil in 1889 and eye movement abnormalities are mentioned, although a supranuclear lesion is not documented clinically \( (17,18) \) (see Fig. 3). This case also had highly asymmetric rigidity of the extremities, a feature more reminiscent of corticobasal degeneration than progressive supranuclear palsy (see next subheading). In this case, the extended neck posture was graphically emphasized:

The face is masked, the forehead wrinkled, the eyebrows raised, the eyes immobile. This facies, associated with the extended posture of the head and trunk, gives the patient a singularly majestic air \( (17,18) \).

With clinical features reminiscent of both progressive supranuclear palsy and corticobasal degeneration, this patient was mentioned in several articles from the Salpêtrière school, although no autopsy was apparently performed.

In their studies of tremor and Parkinson’s disease, Charcot and contemporary colleagues described several other cases of parkinsonian patients who never suffered with either prominent resting or postural tremor. Although the descriptive details are often cursory, several of these cases may well represent cases of progressive supranuclear palsy. Bourneville published two cases in 1876 \( (19) \), and later French students chose this subclass of patients for special clinical emphasis \( (20) \). In his thesis on