

Chapter 1

The Dopaminergic and Non-Dopaminergic Features of Parkinson's Disease

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The dopamine story

Parkinson's disease (PD) is a common age-related neurodegenerative disorder, second only to Alzheimer's disease (AD). It is named in honor of James Parkinson, who provided a description of the disorder in his classic monograph written in 1817 [1]. Clinically, the disease is characterized by a series of cardinal motor features which include resting tremor, rigidity, bradykinesia, and gait impairment with postural instability. The hallmark pathologic features of the disease were described in the early twentieth century and are highlighted by degeneration of neurons in the substantia nigra pars compacta (SNc) coupled with proteinaceous Lewy bodies [2]. The presence of the brainstem dopaminergic system was first described by Dahlström and Fuxe [3]. The importance of dopamine depletion in the pathophysiology of PD was suggested in the late 1950s by Carlsson and colleagues, who showed that inhibition of dopamine uptake by reserpine led to a Parkinson-like syndrome in rabbits that could be reversed with the dopamine precursor levodopa [4]. Shortly afterwards, Ehringer and Hornykiewicz identified that there was a profound dopamine deficiency in the striatum of patients with PD [5]. It was subsequently established that dopamine is not simply a precursor in the norepinephrine pathway, but is itself a neurotransmitter that is manufactured in SNc neurons and transported to the striatum by way of the nigrostriatal tract.

Based on these observations, it was hypothesized that dopamine replacement might be an effective treatment strategy for PD. Dopamine itself does not cross the blood-brain barrier, so interest focused on the dopamine precursor levodopa, which can gain entry into the brain via the large neutral amino acid transport pathway and can then be decarboxylated to form dopamine. Initial studies in the early 1960s reported a dramatic benefit with small doses of levodopa [6], but these results were sur-

prisingly difficult to confirm in early trials. It was not until the reports by Cotzias and co-workers in 1967 and 1969 that it was appreciated that consistent benefits could be obtained with relatively higher doses of levodopa [7,8]. These results were subsequently confirmed in double-blind trials [9], and the levodopa era had begun. Although levodopa provided benefit for the vast majority of PD patients, therapy was complicated by nausea and vomiting and could not be tolerated by as many as 50% of individuals. This problem was found to be due to the peripheral accumulation of dopamine and activation of dopamine receptors in the nausea and vomiting center of the brain (area postrema) that are not protected by the blood-brain barrier. This problem was resolved by administering levodopa in combination with a peripherally acting dopamine decarboxylase inhibitor [10], and levodopa today is routinely administered in combination with the decarboxylase inhibitor carbidopa (Sinemet[®]) or benserazide (Madopar[®]). Since its introduction, levodopa has been the standard of care for PD and has benefited millions of patients throughout the world. Virtually all patients improve, and benefits have been noted with respect to the classic motor features of the disease, quality of life, independence, employability, and mortality [11].

Levodopa-induced motor complications

Shortly after its introduction, it became appreciated that chronic levodopa therapy is associated with a series of motor complications, primarily comprised of fluctuations in motor response and involuntary movements or dyskinesias [12] (see Box 1.1). A review of the literature suggests that as many as 90% of patients who have received levodopa therapy for up to 10 years experience motor complications [13]. In severe cases, motor complications

Box 1.1 Levodopa-induced motor complications

Motor fluctuations

- Wearing-off episodes
- Delayed on
- No “on”
- On/off phenomenon

Dyskinesia

- Peak dose dyskinesias
- Diphasic dyskinesia
- Dystonia

can be disabling and patients can cycle between “on” periods complicated by troublesome dyskinesias and “off” periods associated with severe parkinsonism and sometimes painful dystonia. This can result in severe disability for these patients and limit the utility of levodopa treatment.

The mechanism responsible for levodopa-induced motor complications in PD is not known. Levodopa does not cause motor complications in normal individuals, and the risk of their occurrence is increased with greater degrees of disease severity. Population studies and clinical trials indicate that motor complications are associated with the use of higher doses of levodopa [14,15], and they do not seem to be as troublesome today as they were a decade ago when physicians routinely employed higher doses. There is also evidence suggesting that the development of motor complications may relate to non-physiologic replacement of brain dopamine with standard formulations of levodopa [16]. In the normal state, SNc neurons fire continuously, striatal dopamine is maintained at a relatively constant level, and striatal dopamine receptors are continuously activated. With disease progression, as the striatum becomes progressively denervated, striatal dopamine levels become increasingly dependent on peripheral levodopa availability. Levodopa is typically administered to PD patients with a frequency of two to four times per day. As levodopa has a relatively short half-life (60–90 min), this intermittent administration of levodopa does not restore dopamine in a continuous and physiologic manner and leads to discontinuous or pulsatile stimulation of dopamine receptors. This in turn has been shown to result in molecular changes in striatal neurons, physiologic changes in pallidal neurons, and ultimately motor complications. It is now considered that the altered patterns of receptor stimulation by exogenously administered levodopa contribute to the development of motor complications in PD patients.

Over the past several decades, a number of interventions have been introduced to treat or prevent

levodopa-induced motor complications by enhancing or prolonging the dopaminergic effect [17]. Dopamine agonists act directly on dopamine receptors and have longer half-lives than levodopa, MAO-B inhibitors block dopamine metabolism and increase synaptic dopamine concentrations, and COMT inhibitors block the peripheral metabolism of levodopa, thereby increasing brain availability of the drug. Each has been shown to reduce off-time in fluctuating patients. In addition, the early introduction of long-acting dopamine agonists reduces the risk of dyskinesia in comparison with levodopa and permits lower doses of levodopa to be employed. Surgical therapies that target nuclei within basal ganglia circuitry that have abnormal firing patterns associated with chronic levodopa treatment in PD have been shown to provide dramatic improvements for both motor fluctuations and dyskinesias [18]. Similar results have been reported with continuous infusion of dopaminergic agents such as levodopa and dopamine agonists [19,20], although these therapies have not yet been adequately evaluated in double-blind trials. It is noteworthy that no therapy has as yet been shown to provide anti-Parkinsonian benefits that are superior to what can be achieved with levodopa alone. Amazingly, 40 years after its introduction, levodopa remains the most effective symptomatic treatment for PD and the “gold standard” against which new therapies must be measured.

In the modern era, motor complications are not the problem they were a decade ago. This is related to the use of lower doses of levodopa, initiation of therapy with agents such as dopamine agonists that are less prone to induce motor complications, the availability of multiple medications that treat wearing-off effects, and surgical therapies that can control even severe motor complications. Research studies have examined the potential of dopamine cell transplantation or gene therapy strategies designed to restore the dopamine system in a physiologic manner, but benefits have not been observed in double-blind controlled studies and new research protocols continue to be explored. There is also an intensive effort to try to develop long-acting oral treatment strategies that can provide the benefits of levodopa without motor complications [21]. It is therefore realistic to consider that, in the not too distant future, we will be able to restore dopamine function to patients with PD and satisfactorily control the dopaminergic features of the disease for the vast majority of patients.

The non-motor and non-dopaminergic features of PD

Although treatment of the dopaminergic features has markedly changed the quality of life for most patients with PD, they continue to suffer from disability related

to features that do not respond to levodopa. These are known as the non-dopaminergic features of PD because they likely relate to pathology that involves non-dopaminergic systems. It is now widely appreciated that pathology in PD involves more than just the nigrostriatal dopamine system. Neurodegeneration with Lewy bodies can be found in cholinergic neurons of the nucleus basalis of Meynert (NBM), epinephrine neurons of the locus coeruleus (LC), and serotonin neurons of the median raphe, in addition to neurons in the olfactory system, cerebral cortex, spinal cord, and peripheral autonomic nervous system [2,22]. Studies by Braak *et al.* based on α -synuclein immunostaining further suggest that in many PD patients pathologic changes occur in a progressive manner, beginning first in non-dopaminergic neurons of the dorsal motor nucleus of the vagus (DMV) and olfactory systems, involving dopamine neurons in the mid-brain only in the mid-stage of the illness, and ultimately extending to involve the cerebral cortex in the later stages of the disease [23]. Although this precise sequence of Lewy pathology may not be found in all patients [24], and does not explain cases of dementia with Lewy bodies (DLB) where dementia is the presenting manifestation, it now seems likely that in most patients Lewy body pathology develops in non-dopaminergic regions of the nervous system before the dopamine system. Indeed, there is evidence of Lewy body pathology in autonomic neurons of the heart, gastrointestinal system, and cervical sympathetic ganglia in individuals with no clinical evidence of parkinsonism [25,26].

The non-dopaminergic clinical manifestations of PD are summarized in Box 1.2. These features, and particularly the non-motor manifestations, are frequently unrecognized and go untreated in as many as 50% or more of patients [27,28]. This is extremely relevant, as non-motor features have been shown to be a major determinant of the quality of life of PD patients and their caregivers [29–31]. In this respect, the 15 year follow-up from the prospective Sydney multicenter study is illuminating. Although 95% of patients experienced motor complications, it was the non-dopaminergic features of PD, such as falling, freezing, and dementia, that were the predominant causes of disability [32]. Indeed, 80% of surviving patients had experienced falls, with 23% suffering fractures, and 80% had dementia, with 50% being sufficiently severe to meet DSMIVR criteria. These non-dopaminergic features are also the main determinants of the need for nursing home placement [32–34] and survival [35,36] for PD patients.

The frequency with which non-motor features occur in PD is illustrated by recent studies which used newly developed questionnaires and scales to seek non-motor features in consecutive PD patients [37,38]. They illustrate that these symptoms occur far more frequently in PD patients than in age-matched controls, are present at the earliest stages of the illness, and gradually increase

Box 1.2 The non-dopaminergic features of PD

- *Motor disturbances*
 - Gait dysfunction, freezing and postural instability
 - Dysphagia
 - Drooling
- *Sensory disorders*
 - Pain and paresthesia
 - Anosmia
 - Visual discrimination defects
 - Ageusia
- *Autonomic dysfunction*
 - Orthostatic hypotension
 - Gastrointestinal disturbances – constipation, incontinence
 - Urinary impairment
 - Sexual dysfunction
 - Sweating
- *Sleep disturbances*
 - Sleep fragmentation
 - Excess daytime somnolence
 - Vivid dreaming
 - Insomnia
 - REM behavior disorder
 - RLS and periodic limb movements
 - Sleep apnea
- *Mood disturbances*
 - Depression
 - Anxiety and panic attacks
 - Apathy
- *Neuropsychiatric*
 - Hallucinations, illusions, delusions
 - Impulse control disorders
- *Cognitive impairment and dementia*
- *Others*
 - Seborrhea
 - Dry eyes
 - Fatigue
 - Diplopia
 - Blurred vision
 - Weight loss

in number and severity over time in concert with the progression of the classical motor features of the illness. Different series show a broad range of prevalence of non-motor features in PD [35,37,39], probably due to the different methods used to assess and identify these features. It is estimated that between 50 and 100% of PD patients exhibit or are affected by non-motor features during the course of their disease [40]. In a cross-sectional population study, only 2.4% of PD patients reported not having non-motor symptoms, with milder PD patients reporting eight different types of symptoms compared with 12 in more

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severely affected patients [37]. Collectively, these studies illustrate the importance of non-dopaminergic and non-motor features in PD patients. The natural history of non-dopaminergic and non-motor features in PD is not well studied, and a large, longitudinal multicenter study is needed to assess formally the natural progression and risk factors for the development of these features in PD. The PRIAMO (PaRkInson And non Motor symptOms) study is ongoing and is expected to provide a better definition of the nature, extent, and relative importance of non-motor features in the PD population [41].

In keeping with the pathologic findings of Braak *et al.*, there is also evidence suggesting that many non-dopaminergic features, such as anosmia, constipation, and REM behavior disorder, may antedate the development of the classical dopaminergic motor features of PD [42–44]. Langston has suggested that patients who experience this triad of non-dopaminergic features are not just at risk for developing PD, but may actually have an early form of the disease [45]. Indeed, neuroimaging studies in at-risk populations have shown reduced dopaminergic activity [46], suggesting they may well be in an early phase of the disease consistent with this hypothesis. Originally, the term “preclinical” features was applied to these symptoms, but recognizing that they likely represent the earliest clinical manifestations of the disease, the term “premotor” PD is probably more accurate.

It should be appreciated that although non-motor features of PD may not be influenced by levodopa therapy, there can be fluctuations in association with doses of levodopa or dopamine agonists – this suggests that there may be a dopaminergic component to some of these non-motor features. For example, in some patients “off” periods are associated with pain, panic attacks, severe depression, confusion, sense of death, dysphagia, sweating, and/or difficulty with micturition and passing stool [47]. These symptoms can sometimes be improved, even dramatically, with levodopa or dopamine agonist therapy. Thus, non-motor features cannot be classified as being purely non-dopaminergic.

Importance of the non-dopaminergic features of PD

While the classical dopaminergic motor features continue to define PD, it is clear that we are entering a new era in which the non-dopaminergic features of the disease are being identified with increasing frequency and are an important source of disability for many individuals. In an age when PD patients had untreatable tremor, rigidity, and bradykinesia, the non-dopaminergic features of the illness were less evident and seemingly less important. Today, however, the classical motor features can usually be well controlled with dopaminergic therapies, and non-dopaminergic features have become increasingly problematic. Indeed, non-dopaminergic problems such as freezing, falling, and dementia, which cannot

be adequately treated with dopaminergic therapies, are the major source of disability for patients with advanced PD. Research into their pathophysiology and the development of effective treatment strategies to control them are urgently required. Much of current research, particularly in areas such as cell-based and gene therapies, continues to be primarily focused on the dopamine system. Although this research is laudatory, it is currently not easy to conceive (although not inconceivable) how better restoration of the dopamine system will restore function to disabilities primarily related to degeneration of non-dopaminergic neurons. Clearly, more attention needs to be focused on the nature of non-dopaminergic pathology and the potentially disabling symptoms that ensue. Further, the evolution of the PD process to include these disabling problems emphasizes the need for neuroprotective therapies in PD that might be introduced early in the course of the disease to slow or stop disease progression and thereby potentially prevent their occurrence.

Non-dopaminergic features might also be important in facilitating the development of a neuroprotective therapy. In the laboratory, we routinely test promising agents in models of PD such as the MPTP monkey and the 6-OHDA lesioned rat, which primarily reflect dopamine depletion. They do not, however, replicate the pathologic or behavioral spectrum of the disorder. More importantly, there is no assurance that the etiopathogenesis of cell death in these models is in any way related to PD, or that agents that are protective in these models will prove beneficial in PD [48]. There is an intense effort to develop new models that more faithfully replicate the pathology of PD with involvement of the non-dopaminergic systems. Such a model might not only permit the development of therapies to treat non-dopaminergic features of PD, but might reflect a mechanism that more closely represents what is actually going on in PD than do current models. Unfortunately, the development of such models has not proven easy. It is hoped that the development of transgenic animals which carry gene mutations associated with PD might accomplish this goal, but to date this has proven to be difficult to achieve and further efforts are required.

Non-dopaminergic features of PD might also serve as primary endpoints in clinical trials seeking to identify a neuroprotective or disease-modifying therapy. Agents tested in studies performed to date cannot be definitively interpreted to have provided a neuroprotective effect even if the trial is positive, because a confounding symptomatic or pharmacologic effect of the study intervention cannot be excluded [49]. For example, it may not be possible to be sure whether positive results are due to the study agent slowing disease progression or to the agent having a symptomatic effect that merely masks ongoing neurodegeneration. Non-dopaminergic features of PD are defined by their lack of response to dopaminergic therapies, perhaps making them more suitable for endpoints than the classic motor features which have

traditionally been employed to date. Even if neuroprotection cannot be definitively established, a determination that a given intervention slows or prevents the emergence of disability related to non-dopaminergic features for which there is currently no adequate therapy would be a welcome addition regardless of its mechanism of action. A composite endpoint that incorporates conventional UPDRS scores along with measures of non-dopaminergic features such as falling, freezing, and dementia is being employed as the primary outcome measure for an NIH-sponsored long-term simple study that aims to assess the effect of an intervention on cumulative disability. Although such studies are usually relatively long (approximately 5 years), the inclusion of non-dopaminergic features in the primary endpoint may provide greater insight into the effect of a new study drug on disease progression than current outcome measures.

Finally, if a neuroprotective therapy that slowed the rate of disease progression could be identified, early diagnosis would be extremely important. Non-dopaminergic features might permit the diagnosis of PD to be made prior to the emergence of the classical motor features of the disease, and thus permit a disease-modifying agent to be introduced at an earlier time point. Already, there is evidence suggesting that early treatment with a given agent might provide benefits that cannot be achieved by later treatment with the same agent, possibly by preserving beneficial compensatory mechanisms or preventing the development of maladaptive compensatory mechanisms [50,51,51a]. Early diagnosis, and the early introduction of therapy, have therefore become a major consideration in the current management of the early PD patient [52].

Conclusions

Interest in PD during the past half century has primarily focused on the dopamine system. However, it is evident that PD is a disorder with widespread pathology that involves more than just the nigrostriatal system. Clinical features of PD reflect this non-dopaminergic pathology and it is now appreciated that many disabling features of the disease do not respond to or are not adequately controlled by dopaminergic therapies. In a way, we are victims of our own success. Our ability to control the classical motor features of the illness with dopaminergic therapies has highlighted the importance of the non-dopaminergic features of the disease. Indeed, in the levodopa era, the non-dopaminergic features of PD constitute the major source of disability for advanced PD patients and their treatment constitutes an important unmet medical need. It is interesting to speculate on whether the same will hold true for other degenerative diseases such as AD and ALS once a satisfactory treatment for the primary cognitive and motor aspects of these illnesses has been developed.

Over the decades, there have been many textbooks that have addressed the clinical, pathologic, and etiopathologic features of PD, particularly as they relate to the dopamine system. We believe that there is now sufficient information and interest to warrant a full textbook dedicated to the non-dopaminergic features of PD. Here, we have gathered together a comprehensive series of chapters on the various clinical, pathologic, and scientific issues related to the non-dopaminergic aspects of PD written by a group of experts in their various fields. It is hoped that better recognition and understanding of the origin of these problems will lead to enhanced patient care and serve as a stimulus for the development of newer and more effective therapies for PD patients.

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