Overview of the Extranigral Aspects of Parkinson Disease

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In recent years, there has been increasing recognition of the features of Parkinson disease that are not related to nigrostriatal dopamine deficiency. This review addresses selected clinical, anatomic, pathologic, and biochemical correlates of the early premotor symptoms of Parkinson disease, later nonmotor fluctuations, and advanced dopa-unresponsive motor and nonmotor features. The recognition of early features that predate classic motor symptoms will be important as effective neuroprotective therapy becomes available. Later-stage features often contribute markedly to disability and impaired quality of life and, therefore, represent an important future therapeutic challenge.

Loss of substantia nigra pars compacta (SNc) dopaminergic neurons is considered to be the most important neuropathologic hallmark of Parkinson disease (PD). Focus on the nigrostriatal dopaminergic system is justified by the prominent motor manifestations for which patients seek treatment and the remarkable success of dopamine replacement therapy. However, it has become increasingly apparent that the neuropathologic changes of PD extend well beyond the nigrostriatal system (Figure). Even components of the early core motor symptoms may not be exclusively related to nigrostriatal dopamine deficiency. This is particularly the case for tremor for which animal models and clinical, pharmacologic, positron emission tomography, and postmortem studies support an important role for extranigral mechanisms (Table 1).¹ Most of the disability brought on by advancing PD relates to the emergence of symptoms that respond poorly, if at all, to levodopa or modern surgical therapies; these disabilities include “on”-medication axial motor features such as gait freezing, postural instability with falls, dysarthria and dysphagia, and a broad spectrum of nonmotor symptoms. Nonmotor symptoms comprise a variety of neuropsychiatric, autonomic, sensory, and sleep disorders. Although some of these symptoms, such as dementia and psychosis, typically appear late in the course of the disease, other nonmotor symptoms may occur early in the disease, even before the onset of motor problems, and many continue to be common across all stages of PD. Although the anatomic, pathologic, and biochemical substrates for much of the PD symptom complex are yet to be fully characterized, significant progress has been made. Pathologic changes occur in widespread regions of the central and peripheral nervous systems, and it is recognized that many different neurotransmitter systems (eg, noradrenergic, serotonergic, and cholinergic) in addition to dopamine are deranged as part of the multisystem neurodegeneration that constitutes PD. Increasing evidence suggests that in most cases the first neurons affected in PD are nondopaminergic, and the SNc may become involved only after the disease is well established in other regions of the nervous system.² Indeed, α-synuclein–containing Lewy bodies (LBs), the histologic hallmark of PD, were first described almost a century ago in the nondopaminergic neurons of the dorsal motor nucleus of the vagal nerve, nucleus basalis of Meynert, and hypothalamus. On the other hand, abnormalities in extranigral dopaminergic systems (mesolimbic, mesocortical, and thalamic) also likely contribute to the PD symptom complex.

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EARLY PREMOTOR FEATURES OF PD

A number of nonmotor features can precede the motor symptoms of PD. These symptoms probably arise from extranigral structures. Two types of studies provide important insights into this issue: (1) the prospective evaluation of individuals who eventually developed overt PD and (2) the evaluation of individuals whose brains show evidence of incidental Lewy body disease (ILBD). The term ILBD is used when LBs and Lewy neurites (α-synuclein inclusions) are found in the central nervous system of individuals without clinically documented parkinsonism or dementia. The distribution of the inclusions, neurochemical changes, and neuronal counts support the hypothesis that ILBD represents preclinical PD (or dementia with LBs), with lack of motor symptoms due to the subthreshold severity of the disease.3

Table 2 lists those features that have been convincingly shown to occur well before the onset of parkinsonism, in some cases preceding it by decades. However, these features are not universally present, and most are so common and nonspecific that they alone could not predict which patients might be in the earliest stages of the disease (for trials of neuroprotective therapies). Olfactory deficits and cardiac sympathetic denervation are present in a high proportion of patients who present with the earliest motor signs, which suggests that such features probably precede the motor signs and may be more useful in characterizing early disease status. Other features documented in a smaller proportion of patients early in the course of the disease include pain, orthostatic hypotension, urinary urgency, and executive dysfunction found on neuropsychological testing.

BRAAK STAGING

The widely cited work of Braak and colleagues emphasizes the importance of early extranigral involvement in PD. Applying modern immunohistochemical techniques to a large autopsy population, these authors proposed a pattern of PD progression.2 Their work suggests that PD generally begins in the anterior olfactory nucleus and medulla (including the dorsal motor nucleus of the vagal nerve) and ascends through the brain in a predictable sequence that eventually involves the entire neocortex. According to this scheme, SNc degeneration does not occur until an intermediate stage (stage 3 of 6 stages) is reached in the temporal sequence of PD, with motor symptoms emerging in stage 3 or 4.

Although the Braak staging scheme with its implications to the premotor features of PD has been largely confirmed by other investigators, several criticisms of this work have been raised. There remains uncertainty regarding the impact of α-synuclein disease on neuronal function and survival. Exclusion of cases of dementia with LBs and the fact that ILBD cases were preselected for the presence of α-synuclein deposition in the dorsal motor nucleus of the vagal nerve raise the possibility of selec-
The early involvement of the anterior olfactory nucleus is a likely cause of hyposmia in PD (and ILBD). In Braak stages 1 and 2, in addition to the anterior olfactory nucleus, lower brainstem structures, including the dorsal motor nucleus of the vagal nerve, locus ceruleus, and raphe nuclei, are involved. The locus ceruleus and raphe nuclei project widespread connections (noradrenergic and serotonergic, respectively) to many brain regions, as well as to the spinal cord. Although the specific cause of rapid eye movement (REM) behavior disorder in PD is unknown, postmortem examination of patients with idiopathic REM behavior disorder has documented severe LB involvement and/or neuronal loss in the locus ceruleus and substantia nigra as the most significant histopathologic findings. The role of γ-aminobutyric acid (GABA) in mediating REM sleep has been recently suggested, with a complex interaction between brainstem noradrenergic and serotonergic neurons, which switch from a REM-on to a REM-off state, depending on the inhibitory effects of GABA. The current treatment of choice for REM behavior disorder is the benzodiazepine clonazepam, which influences GABAergic function. Involvement of the locus ceruleus (1 of several subcortical noradrenergic regions that have wakefulness-promoting actions) is a postulated cause of daytime hypersomnolence occurring early in PD. The association between hypersomnolence and longer PD duration and greater mo-

### Table 1. Possible Clinicopathologic Correlates of Parkinsonian Tremor and Other (Later Stage) Extranigral Features and Treatments

<table>
<thead>
<tr>
<th>Clinical feature</th>
<th>Pathologic Correlates</th>
<th>Treatments</th>
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<tbody>
<tr>
<td>Tremor</td>
<td>Extranigral midbrain (AB) dopaminergic neurons, midbrain raphe</td>
<td>Dopaminergic medications, anticholinergic agents, clozapine, DBS (STN or VIM thalamus)</td>
</tr>
<tr>
<td>Levodopa-related fluctuations in nonmotor symptoms (eg, mood, motivation, and pain)</td>
<td>Mesolimbic and mesocortical dopaminergic neurons, dopaminergic medication-induced plastic changes in these and other pathways</td>
<td>Effective treatment of underlying PD to reduce “off”-medication time; for manic symptoms, ICs, or DDS, reduce dopaminergic medications (additional measures may be required)</td>
</tr>
<tr>
<td>Dopa-unresponsive motor features (eg, postural instability and gait disorder)</td>
<td>PPN, extranigral midbrain (A10) dopaminergic neurons, (postsynaptic) striatal and pallidal neurons, thalamic nuclei, premotor cortical regions (eg, pre-SMA)</td>
<td>Nonpharmacologic, eg, physiotherapy, PPN DBS (experimental)</td>
</tr>
<tr>
<td>Dementia</td>
<td>Subcortical nuclei, including locus ceruleus, medial SNc, VTA, nucleus basalis of Meynert (with severe cortical cholinergic deficit); limbic regions and cerebral cortex</td>
<td>Cholinesterase inhibitors, memantine, hydrochloride</td>
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<tr>
<td>Visual hallucinations</td>
<td>Brainstem nuclei, nucleus basalis of Meynert, hypothalamus, ventral temporal lobe, and other cortical regions</td>
<td>Elimination of less potent antiparkinsonian medications; atypical antipsychotics (clozapine, quetiapine); cholinesterase inhibitors; treat excessive daytime somnolence</td>
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**Abbreviations**: DBS, deep brain stimulation surgery; DDS, dopamine dysregulation syndrome; ICs, impulse control disorders; PD, Parkinson disease; PPN, pedunculopontine nucleus; SMA, supplementary motor area; SNc, substantia nigra pars compacta; STN, subthalamic nucleus; VIM, ventral intermediate nucleus of the thalamus; VTA, ventral tegmental area.

### Table 2. Early Premotor Features of PD

<table>
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<tr>
<th>Symptoms and Type of Study</th>
<th>Risk of Developing Clinical PD (Type A Study) or Having ILBD at Autopsy (Type B Study) and Associations Among Premotor Features (Type C Study)</th>
</tr>
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</table>
| Olfactory deficit         | A OR=5.2 in men with the lowest vs highest 2 quartiles of odor identification ability
g B OR=11 in men with the lowest vs highest tertile of odor identification ability |
| RBD                       | A 38% (parkinsonism) 12.7 years after RBD onset; signs of parkinsonism newly found in 5 of 6 patients with a long history of idiopathic RBD |
| Excessive daytime somnolence | A OR=3.3 in men with excessive daytime somnolence |
| Depression, anxiety       | A HR=3.1 in depressed patients OR=2.4 in patients with depressive and anxiety disorders |
| Constipation               | A RR=2.7 in men with <1 BM per day vs men with 1 BM per day B OR=4.5 in men with <1 BM per day vs men with >1 BM per day |
| Erectile dysfunction       | A RR=3.8 in men with erectile dysfunction vs those with very good function |

**Abbreviations**: BM, bowel movement; HR, hazard ratio; ILBD, incidental Lewy body disease; OR, odds ratio; PD, Parkinson disease; RBD, rapid eye movement behavior disorder; RR, relative risk.

*Variously reported as a percentage, OR, HR, or RR.*
tor severity suggests that progressive involvement of additional structures, such as hypocretin-producing neurons in the hypothalamus (with the hypothalamus affected as early as Braak stage 3), may also be important. Noradrenergic and serotonergic dysfunction may underlie symptoms of depression and anxiety. This theory is supported by older postmortem and cerebrospinal fluid 5-hydroxyindoleacetic acid studies; more recent functional imaging studies using positron emission tomography, single-photon emission computed tomography, and transcranial ultrasonography; and the response of these symptoms to selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors. Positron emission tomography studies also support a role of cortical and subcortical limbic dopaminergic projections in depression. Pathologic changes in the locus ceruleus, raphe nuclei, mesolimbic system, and hypothalamus (as well as in the spinal cord dorsal horn and thalamus) have been postulated to underlie PD-related pain.

Although the Braak staging system does not include a description of LB disease in the spinal cord or peripheral nervous system, neuropathologic studies of PD and ILBD have demonstrated early involvement of autonomic neurons in the thoracic and sacral spinal cord, heart, and gastrointestinal and genitourinary tracts. Cardiac uptake on metaiodobenzylguanidine 123–labeled scintigraphy, a specific marker for noradrenergic transporters, is reduced in nearly all patients with PD, even at the earliest stage of the disease and in idiopathic REM behavior disorder, and cardiac sympathetic denervation is also found in ILBD. In addition, LBs have been found in the lower esophagus and small intestine of nonparkinsonian patients without ILBD in the central nervous system, suggesting that in some cases LB disease may begin outside the brain; this result has also rarely been reported for LBs in the adrenal gland. It is intriguing to consider the possibility that PD may actually begin in the peripheral autonomic nervous system and only later involve the central nervous system.

EXTRANIGRAL FEATURES PERTAINING TO LEVODOPA THERAPY

Most patients experiencing motor fluctuations after long-term oral levodopa therapy also identify nonmotor fluctuations. Symptoms such as anxiety, sadness, slowness of thinking, fatigue, apathy, drenching sweats, urinary urgency, and pain (dystonic or nondystonic), are usually associated with the “off”-medication state, whereas hypomanic symptoms may occur during the “on”-medication state. The response of some but not all of these symptoms to subthalamic nucleus deep brain stimulation suggests varied pathogeneses that involve the basal ganglia motor circuit influenced by this treatment and other areas affected by long-term pulsatile dopaminergic therapy. Antiparkinsonian treatment may also be complicated by the development of impulse control disorders, such as pathologic gambling and shopping, binge eating, and hypersexuality, increasingly recognized problems in treated PD patients. Less commonly, addiction to dopaminergic agents (dopamine dysregulation syndrome [DDS]) is seen.

CLINICOPATHOLOGIC CORRELATES OF NONMOTOR FLUCTUATIONS

The cause of dopamine-induced fluctuations in many of the nonmotor symptoms experienced by PD patients remains unknown. We briefly discuss the possible correlates of motivation and mood changes in PD. In Braak stage 3, the medial SNc and ventral tegmental area become affected, resulting in loss of dopaminergic fibers to the caudate nucleus, nucleus accumbens, amygdala, anterior cingulate cortex, and other limbic and frontal cortical areas where dopamine is essential for mediating mood, working memory, reward-related learning, and motivation. Thus, mesolimbic and mesocortical dopamine deficiency may underlie some of the nonmotor symptoms that occur in the “off”-medication state. On the other hand, it has been postulated that the relative preservation of ventral striatal dopamine, compared with the dorsal striatum, may result in dopaminergic medication-induced overdosing of the ventral striatum in some patients that may increase impulsivity and underlie abnormal reward-driven behaviors, such as impulse control disorders and DDS. For example, Evans et al demonstrated a link between compulsive dopaminergic drug use (as part of DDS) and abnormal (“sensitized”) mesolimbic dopaminergic transmission. Abnormal dopaminergic modulation of the limbic system may also be responsible for levodopa-related fluctuations in mood and pain, symptoms that are often exaggerated in DDS.

EXTRANIGRAL FEATURES OF ADVANCED PD

Dementia, Visual Hallucinations, and Dopa-Unresponsive Motor Disability

Although the effect of levodopa on bradykinesia, rigidity, and tremor remains relatively stable during the course of the disease, the response for axial problems, such as postural instability, gait disorder, and speech impairment, declines. In these patients, the best motor response to a supratreshold dose of levodopa becomes incomplete and insufficient. A related observation is that in most patients with an initial tremor-dominant phenotype, the clinical picture shifts during the disease to a postural instability and gait dysfunction phenotype. This transition is apparently unidirectional and irreversible and is associated with accelerated cognitive decline and a highly increased risk for subsequent dementia, consistent with other studies demonstrating a clear relationship between axial symptoms and cognitive decline in PD. As PD progresses, many patients develop frank dementia. For example, the community-based Sydney multicenter study, which is the longest prospective study of PD, reported a disturbing 83% frequency of dementia 20 years after PD diagnosis (mean age, 74 years); falls, gait freezing, moderate dysarthria, choking, and hallucinations were experienced by 87%, 81%, 81%, 48%, and 74% of patients, respectively. Once dementia was diagnosed, the median survival was 4.5 years. Similarly, Williams and Lees reported that patients have generally passed the halfway mark in the course of their disease when visual hallucinations develop, with a mean survival of 4.4 years after the onset of this symptom.
CLINICOPATHOLOGIC CORRELATES OF ADVANCED PD

In the latter half of the Braak staging scheme, LBs spread into limbic areas (stage 4), cortical association areas (stage 5), and finally primary cortical areas (stage 6). Limbic and cortical LB disease have been shown to be the main morphologic substrates of PD dementia (PDD). However, Braak et al showed that even in stage 3 (ie, in the virtual absence of cortical LB involvement), a third of patients already had impaired cognition, mostly of moderate severity. Conversely, Colosimo et al described a series of PD patients with considerable limbic and/or neocortical LB involvement but without important cognitive impairment. In addition, later-stage cortical involvement generally occurs against a backdrop of the already advanced destruction of vulnerable subcortical nuclei; in autopsy studies, PDD has been associated with neuronal loss in the locus ceruleus, medial SNc, ventral tegmental area, and nucleus basalis of Meynert. Although some authors have emphasized impaired mesolimbic and mesocortical dopaminergic function in PDD, a severe cortical cholinergic deficit, independent of co-existent Alzheimer disease changes, is the most consistent neurochemical finding associated with PDD, and cholinesterase inhibitors are frequently more effective in PDD than in Alzheimer disease. The response of apathy to these agents supports a role for cholinergic systems in this feature of PD as well. Glycinergic and especially glutamatergic factors may also play a role in PDD, although the evidence for this theory is limited. Additional Alzheimer pathologic burden in PDD is generally low but probably exacerbates the overall disease process, as does aging.

The pathologic basis of visual hallucinations in PD may involve the inferotemporal cortex and substantia nigra pars reticulata. The inferotemporal lobe is involved in visual processing of complex features related to people and objects, as is typical in the well-formed hallucinations of PD. Lewy bodies are increased in the ventral temporal lobe in PD patients with well-formed visual hallucinations compared with those without, and cerebral blood flow is reduced in the temporal and upper temporal-occipital cortex compared with PD patients who do not hallucinate. The substantia nigra pars reticulata has been suggested as a potential site of visual hallucinations because lesions in the medial substantia nigra pars reticulata can cause vivid, well-formed hallucinations (peduncular hallucinosis) similar to those of PD. Disturbances in the sleep-wake cycle are also often found in those who hallucinate and may account for the diurnal fluctuations in these symptoms. Such patients may have more daytime somnolence and vivid dreams or nightmares, although the exact nature of this relationship is not entirely clear. Indeed, in some patients hallucinations may relate to intrusions of REM sleep into wakefulness comparable to hypnagogic hallucinations in narcolepsy. Thus, disease in brainstem (and hypothalamic) structures controlling sleep may also cause fluctuating hallucinations in PD. Postmortem studies show a relative preservation of serotonin 2 receptors in the temporal cortex of PD patients with hallucinations compared with PD patients who do not hallucinate. To date, the atypical neuroleptics quetiapine fumarate and clozapine, which are also serotonin 2A and 2C receptor antagonists, are the most effective treatments for hallucinations in PD. A cholinergic component is supported by the response of hallucinations in patients with dementia to cholinesterase inhibitors. The relationship between hallucinations and REM intrusions might also support a role for treating excessive daytime somnolence in these patients.

It is unlikely that the changing motor response to antiparkinsonian drugs (with the development of dopa-resistant features) is solely due to a progressive degeneration of the presynaptic nigrostriatal dopaminergic system. Involvement of extranigral structures is likely to be important. Loss of striatal neurons has been demonstrated in PD, with 1 study reporting the presence of LBs in striatal medium-sized neurons beginning in Braak stage 3; the severity of these striatal changes correlated with the Braak stage. Changes in postsynaptic striatal and pallidal neurons, with a reduction of dopamine D3 receptors, have been associated with the loss of response to dopaminergic drugs. The pedunculopontine nucleus, which is affected in Braak stage 3, is highly interconnected with the basal ganglia and is an important relay nucleus between the basal ganglia and the spinal cord. It plays a role in postural stability and gait (as well as in regulation of the sleep-wake cycle) and is a new surgical target currently being studied in the management of axial signs that fail to respond to levodopa and subthalamic nucleus deep brain stimulation. In later Braak stages, LBs may involve premotor and rarely even primary motor cortex involvement of premotor cortical regions, such as the supplementary motor area or presupplementary motor area, may lead to dopa-unresponsive parkinsonism. Halliday et al demonstrated an 88% loss of presupplementary motor area corticocortical projection neurons in PD patients with severe “on”-medication motor disability.

CONCLUSIONS

Parkinson disease is more than a disease of the nigrostriatal dopaminergic system. The neurodegenerative process affects multiple central and peripheral systems. Currently, optimal symptomatic therapy for PD often consists of a cocktail of agents with diverse pharmacologic actions. This contrasts with usual practice in conditions such as epilepsy, for which monotherapy is the goal. Although dopaminergic therapy remains the mainstay, a wide variety of nondopaminergic agents are also used as highlighted throughout this review. On the other hand, many of these symptoms respond poorly or incompletely to available therapies, further emphasizing the urgency for greater research attention to these problems. The increasing recognition of extranigral aspects of PD will ultimately lead to earlier recognition of the onset of the disease and thus improve effectiveness and use of future neuroprotective therapies. In addition, more effective treatments for many of the disabling nonmotor symptoms and late-stage dopa-resistant motor symptoms will be possible with advances in our understanding of the pathogenesis of these features.
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