Published in final edited form as:

Neurobiol Dis. 2012 June ; 46(3): 505–507. doi:10.1016/j.nbd.2012.04.013.

What *ARE* Parkinson disease? Non-motor features transform conception of the shaking palsy

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Parkinson disease (PD) is one of the most common neurodegenerative diseases of the elderly in the United States and a substantial source of debility, morbidity, mortality, and medical economic costs, despite the fact that the pathogenetic basis of the movement disorder is largely known and rational treatment for the motor symptoms long available. As highlighted here, part of the reason PD continues to challenge researchers and clinicians is that, simply put, PD is not just a movement disorder. Indeed, the non-motor aspects have greater influence on quality of life, institutionalization rates, and healthcare costs (Chaudhuri et al., 2007).

Non-motor features occur in virtually all patients with PD (Weintraub et al., 2008). James Parkinson acknowledged this in his 1817 *Essay on the Shaking Palsy*, when he described gastrointestinal, neuropsychiatric, sleep and cognitive facets (Parkinson, 2002). Nonetheless, to this day it is the motor features that define the diagnosis and constitute the focus of treatment. Non-motor features remain under-recognized, under-researched, and under-treated (Chaudhuri et al., 2005) yet they have important implications for our understanding of the pathophysiologic and pathogenetic natures of PD, potentially opening windows to earlier diagnosis and novel treatment strategies, including disease modification and even prevention.

We now know that the by the time Parkinsonism becomes clinically overt, neurodegeneration has been ongoing for some time. Motor symptoms occur only after the majority of nigrostriatal dopaminergic terminals have been lost and compensatory processes overwhelmed. This has led to the notion of a “pre-motor” phase (Stephenson et al., 2009), during which non-motor manifestations such as cognitive dysfunction, loss of sense of smell, dream enactment behavior, and a variety of autonomic abnormalities may offer key biomarkers of the disease process.

This issue views our understanding of PD through the lens of non-motor features. By studying them we now appreciate the remarkable heterogeneity of conditions that come under the umbrella of PD. This heterogeneity is evident in pathological and clinical laboratory studies, models of pathogenesis, and clinical presentations. It is by now clear that PD involves many neurological systems, resulting in various patterns of Parkinsonian movements, sensory and autonomic dysfunctions, disturbed sleep, and cognitive and psychiatric abnormalities. Within the autonomic domain, several cardiovascular, gastrointestinal, and genitourinary system components evince physiologic and pathologic changes. In general, the non-motor symptoms of PD and related disorders respond poorly if at all to dopaminergic treatments, indicating likely involvement of other neurotransmitters besides the dopamine.

A classic pathologic hallmark of PD is Lewy bodies, intra-cytoplasmic inclusions in brainstem monoaminergic neurons, and a classic neurochemical hallmark is striatal dopamine depletion. We believe there is great scientific and clinical importance in answering the question: How are they linked? In modern terms, the question boils down to the relationship between alpha-synucleinopathy and catecholamine neuronal loss. This issue of *Neurobiology of Disease* includes attempts to address this question.

Lewy bodies and Lewy neurites contain aggregates of the protein α -synuclein, rare families with PD transmitted as an autosomal dominant trait have mutation or replication of the gene encoding alpha-synuclein, and genome wide association studies have consistently reported statistical associations between genotypic variations of the alpha-synuclein gene and PD (Valente et al., 2011). The exact functions of α -synuclein in the neuronal economy remain incompletely understood, although there is evidence that α -synuclein plays roles in synaptic membrane functions, catecholamine biosynthesis, and exocytosis (Dikiy and Eliezer, 2011).

PD pathology has been observed in neurons of the central autonomic network, including the hypothalamus (Wakabayashi and Takahashi, 1997), dorsal motor nucleus of the vagus (Braak et al., 2004), and pre-ganglionic sympathetic neurons of the intermediolateral spinal cord (Braak et al., 2007). PD pathology in post-ganglionic neurons has also been found in several end-organs including the submandibular gland, lower esophagus, duodenum, pancreas, bronchus, larynx, epicardium, adrenal medulla, parathyroid, and ovary (Beach et al., 2010). Although often seen in the absence of neuronal loss (Braak et al., 2007), α -synuclein aggregation seems to be a precursor to the motor disorder in PD (Orimo et al., 2008). According to the Braak hypothesis, before involvement of midbrain substantia nigra dopaminergic neurons, alpha-synuclein deposition occurs in a centripetal, retrograde manner in peripheral monoaminergic neurons and ascends in the brainstem.

Pathological evidence for early involvement of the autonomic nervous system comes from studies of incidental Lewy body disease (ILBD). ILBD is a post-mortem pathological diagnosis based on Lewy-related pathology in the substantia nigra or pontine locus ceruleus (the main source of norepinephrine in the brain) without a clinical history of Parkinsonism during life. It is thought that ILBD may reflect early PD. In 70–100% of ILBD cases, pathological findings in the sacral and thoracic segments of the spinal cord as well as paravertebral sympathetic ganglia resemble those in PD. ILBD also entails involvement of autonomic innervation in several organ systems reviewed in this issue including the cardiovascular, urinary, and gastrointestinal systems (Bloch et al., 2006; Klos et al., 2006). This suggests a spectrum of clinical and pre-clinical signs of synucleinopathies, which historically were recognized only by Parkinsonism and if responsive to dopaminergic treatment classified as PD.

Gastrointestinal symptoms can be prominent and disabling non-motor aspects of PD. Chronic constipation can precede motor signs by several years. Other gastrointestinal symptoms include drooling (due to reduced swallowing), diminished salivary secretion, dysphagia, nausea, early satiety, pain or gastrointestinal bleeding from peptic ulcer, and defecatory dysfunction (Cersosimo and Benarroch, 2012). Cersosimo and Benarroch in this issue review gastrointestinal symptoms and relate them to pathophysiologic changes seen in

PD. α -Synuclein inclusions in the enteric nervous system, sympathetic and parasympathetic autonomic ganglia, and dorsal motor nucleus of the vagus, in both PD and ILBD, seem to follow a rostrocaudal gradient within the gastrointestinal tract, with α -synuclein inclusions being found most frequently in the submandibular gland and lower esophagus, followed by the stomach, small intestine, colon, and rectum. Such a pattern corresponds with vagal innervation. The pathophysiology of gastrointestinal symptoms in PD is likely to be multifactorial, involving abnormalities in reflexes and central pattern generators as well as autonomic outputs and enteric nerves.

Urinary frequency and urgency are typical other non-motor manifestations that can be quite disruptive. Regarding bladder dysfunction in PD, Sakakibara et al. highlight the altered dopamine basal-ganglia frontal circuit that may contribute to detrusor overactivity (Sakakibara et al., 2010).

Cardiovascular dysautonomia illustrates especially graphically the heterogeneity seen in PD and related disorders. PD with orthostatic hypotension (~30–40% of PD cases) and PD without OH seem to be distinctive pathophysiologic subtypes. Jain and Goldstein describe multiple mechanisms involved in PD with orthostatic hypotension, including loss of cardiac sympathetic noradrenergic nerves, partial loss of extra-cardiac noradrenergic nerves, and baroreflex–cardiovagal and baroreflex–sympathetic neurocirculatory failure (Jain and Goldstein, 2012). Cardiac sympathetic denervation occurs virtually universally in PD, independently of the movement disorder or neuroimaging evidence of striatal dopamine depletion. Perhaps surprisingly, cardiac sympathetic denervation in PD is associated with other non-motor manifestations besides orthostatic hypotension, including anosmia, REM sleep behavior disorder, and dementia.

The olfactory bulb is one of the earliest regions demonstrating α -synucleinopathy in PD. In his review here, Doty describes how olfactory disturbance may be considered a pre-motor marker of PD, based on longitudinal studies demonstrating olfactory deficits preceding motor signs of PD by several years and on the increased prevalence of olfactory dysfunction in asymptomatic first-degree relatives of PD patients. Whereas olfactory dysfunction in PD is fairly stable over time and relatively independent of the severity of Parkinsonism (Doty, 2007), it is closely related to losses in cardiac sympathetic function in PD.

REM sleep behavior disorder (RBD) is identified by dream enactment behavior and loss of the normal limb muscle atonia that attends REM sleep. Postuma and colleagues note that RBD is linked to lesions in pontomedullary brainstem structures and associated with future development of neurodegenerative diseases, most often a form of synucleinopathy, the most common of which is PD. Risk estimates for later development of PD among RBD patients may be as high as 65% at 10 years — the strongest known predictor of a neurodegenerative disease. RBD is not easily diagnosed, however, and it is likely most individuals with this disorder do not present to physicians. In PD, RBD is associated with more cognitive impairment, less tremor, and more autonomic dysfunction than PD without RBD (Postuma et al., 2012).

Non-motor features seem to reflect widespread central nervous system pathology, as evidenced by cognitive affective components. It is apparent from Pagonbarraga and Kulisevsky's review that whereas most PD patients have cognitive impairment eventually, specific deficits, severity, and progression to dementia vary substantially. Early in the course of PD, executive dysfunction, visuospatial defects, and memory deficits are common, with a subset experiencing language deficits. Later in PD, dementia is common. Complicating cognitive assessment in PD are other non-motor symptoms such as apathy, anxiety, depression, and daytime sleepiness. Major differences in the rate of cognitive decline within PD suggest subgroups: slow progression with fronto-striatal deficits (attention, memory, search strategies, verbal fluency) and more rapid progression with posterior-cortical deficits (visuospatial and memory deficits such as naming or copying). It is possible that fronto-striatal defects are more related to dopaminergic systems, whereas post-cortical deficits are linked to degeneration of non-dopaminergic fibers (Llebaria et al., 2010).

The presentations in this issue reinforce the notion that dopamine is not the only neurotransmitter affected in PD. Several non-motor aspects are more closely linked to serotonergic, noradrenergic, and cholinergic systems. In their review of psychosis, apathy, depression, and anxiety, Schrag and Gallagher mention non-motor roles of dopamine and Lewy formation in serotonergic raphe nuclei and in the noradrenergic locus coeruleus, possible explanations for occurrence of depression, anxiety, and cognitive dysfunction during the premotor phase (Schrag, 2004).

Cersosimo and Benarroch mention how Braak et al. formulated the hypothesis that an exogenous pathogen may gain entry through peripheral nerve endings through the olfactory epithelium and gastrointestinal mucosa, trigger local abnormal α -synuclein processing, and then pass from neuron to neuron in a prion-like fashion (Braak and Del Tredici, 2008). Some non-motor aspects of PD, however, seem independent of the amount of α -synuclein deposition, perhaps suggesting that different pathogenetic mechanisms converge in the degenerative process. Ferrer and colleagues review implicated processes including impaired synaptic function and plasticity, reduced cerebral glucose metabolism, mitochondrial dysfunction, oxidative damage, altered expression of ribosomal protein mRNA and micro-RNA, altered protein expression in the neocortex, altered lipid composition of cortical membranes, impaired proteosomal function, and glial cell pathology (Ferrer, 2011). Jain and Goldstein (2011) discuss how impaired vesicular uptake of catecholamines may lead to increases in cytosolic metabolites that oligomerize α -synuclein.

It is clear non-motor features are transforming clinical and mechanistic understanding of PD. Taken together, the reviews in this issue raise several important issues. First, PD as currently defined has immense heterogeneity. The fact that non-motor aspects seem to cluster together independently of the severity of nigrostriatal dopamine deficiency and motor features suggest the existence of pathophysiologically distinct PD subtypes. Second, this heterogeneity may reflect differential involvement of several processes and neurotransmitter systems. Third, any *single* non-motor feature is likely to be limited in its utility as a marker for early diagnosis or tracking disease progression. Fourth, PD progression is currently defined by degree of motor disability, which is not associated with progression of non-motor features that may begin prior to or after the onset of motor features. If we accept that non-

motor aspects are intrinsic part of PD, then should our measures of disease progression reflect both motor and non-motor features? If yes, then perhaps patterns of multiple biomarkers or clinical evaluations reflecting both motor and non-motor features should be employed for PD detection and tracking. The development of treatment strategies that encompass non-motor features would greatly reduce the burden of PD.

We see this perspective emerging with the development of animal models of PD that incorporate non-motor facets of PD. In their review, McDowell and Chesselet discuss how both toxin-induced and genetic animal models demonstrate depression, anxiety, cognitive deficits, gastrointestinal function, sleep disturbances, olfactory deficits, and cardiovascular dysautonomia (McDowell and Chesselet, 2012). As concepts of PD evolve to incorporate its essential heterogeneity, a challenge for both clinical and basic researchers will be consider more the integration of central and peripheral non-motor with motor systems in PD.

Acknowledgments

We thank the Editor-in-Chief, Dr. Timothy Greenamyre for the opportunity to edit this special issue and the many patients who have provided important insights. This work was in part funded by NIH grant 1K23 NS070867.

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