The Many Faces of Parkinson’s Disease

By Sarah Horn, M.D., and Howard Hurtig, M.D.

Editor’s Note: The total cost of Parkinson disease (PD), which affects nearly 1 million people in the US is $52 billion every year, with $25.4 billion attributable to direct medical costs such as hospitalizations and medication, and $26.5 billion in non-medical costs like missed work, lost wages, early forced retirement, and family caregiver time. The more we know about PD’s non-motor symptoms—depression, dementia, fatigue, and others—the better we can treat, and perhaps find a cure, for this neurological disorder.
While people usually regard Parkinson’s disease (PD) as a disorder characterized by abnormalities of the brain’s motor functions (movement), such as tremor, stiffness, and difficulties with balance and walking, there is less public awareness that non-motor features, such as cognitive impairment, are equally important. At some point during the long course of this progressive disorder, most patients will be confronted with one or more non-motor symptoms, some of which develop during the premotor or prodromal stage of the illness, when a loss of neurons is accumulating throughout the nervous system before the onset of the classic motor symptoms. Understanding the full range of motor and non-motor features of PD can alert people to recognize the earliest phases of PD and thereby proactively begin a partnership with a health care provider (usually a neurologist) to develop a comprehensive plan of management.

In 1817, the British neurologist James Parkinson, in his essay The Shaking Palsy, accurately described through casual observation the same motor signs and symptoms of PD that we see today. He would never learn about the disease’s non-motor abnormalities, nor would he believe that intellect was affected. Much has changed in 200 years, but only in the last two decades has it become clear that non-motor features are an integral to the pathophysiology of PD. Such features have in fact become defining markers of the disease process, particularly during the prodromal stage of the disease.

The recognition of PD as a common neurological disorder—caused by a lack of the chemical dopamine in the brain—has been bolstered by its prevalence among celebrities, including Muhammad Ali, Michael J. Fox, Linda Ronstadt, Pope John Paul II, and more recently Jesse Jackson and Alan Alda. The average age at diagnosis is 62.5 years, and an estimated 10 percent of patients are diagnosed at age 50 or younger. Although the course of PD extends over many years, the rate of progression is highly variable among individuals. The reasons for this variability are unknown but may be the result of genetic influence. Criteria for the diagnosis of PD to distinguish it from other less common and more rapidly progressive “parkinson syndromes” that resemble it are well established. Some features of PD not usually found in the other disorders include: a prominent rest tremor, a robust response to the standard anti-parkinson drug carbidopa/levodopa (which is converted to dopamine in the brain), certain non-motor symptoms, and a family history of PD. The last of these suggests that one or more of the many recently discovered rare genetic mutations associated with the disorder is implicated.
Analysis of the post-mortem brain is the gold standard for a definitive diagnosis of any neurodegenerative disease. Therefore, every clinical diagnosis of PD or another parkinsonian syndrome during life must be considered probabilistic. Diagnostic errors are common.

Below are the categories of symptoms that characterize non-motor PD in the prodromal or pre-motor phase and the post clinical phase.

**Prodromal non-motor features of PD**
- Loss of sense of smell or olfaction (hyposmia, anosmia)
- Disturbed sleep (Rapid Eye Movement sleep behavior disorder)
- Decreased gastrointestinal motility (constipation)
- Impaired autonomic function (low blood pressure, sweating, urinary frequency)
- Depression

**Post clinical non-motor features of PD**
- Anxiety, apathy, fatigue
- Cognitive impairment and dementia
- Psychosis (hallucinations and delusion)
- Impaired swallowing (dysphagia)
- Pain and sensory disturbances
- Drooling (sialorrhea)
- Dry eyes

Some of the above symptoms listed, by convention, as non-motor actually are the result of motor dysfunction. For example, impaired swallowing is a common late-stage symptom that derives from uncoordinated contraction of muscles in the throat and esophagus. Likewise, dry eyes occur because of decreased blinking; drooling occurs because saliva accumulates due to slowed contraction of the muscles involved in swallowing.

**The Neuropathology of PD**

In 1912, [Frederick Lewy](https://en.wikipedia.org/wiki/Frederick_Lewy), a German neuropathologist, was the first to locate the microscopic pathology of PD in a region of the lower brain or brainstem known as the substantia nigra. He
identified a particular inclusion body—an intracellular clump of protein, later designated a Lewy body—in cells considered to be moribund but not yet dead. For many years, the Lewy body was considered a necessary finding for a pathological diagnosis of PD at autopsy.

Things changed in 1997, when investigators at the National Institutes of Health, using the technique of immunostaining, identified the normal cellular protein alpha synuclein (SYN) in the parkinson brain as a marker for the pathology of PD, not only in substantia nigra Lewy bodies, but in other neurons as well. Subsequent research has shown that normal SYN is converted somehow to become a pathologic agent—perhaps as a result of one or more genetic mutations—and is first deposited in the brainstem below the substantia nigra, where it has no overt clinical impact during the prodromal stage of the disease. As pathologic SYN spreads slowly and more neurons die bottom up, the process arrives at the substantia nigra in the upper brainstem, where cumulative cell death exceeds a critical threshold of cellular attrition and motor symptoms emerge. It has long been known that an estimated 50-60 percent of the dopamine-producing neurons in the substantia nigra will die during the prodromal stage. The process continues its upward migration to the cerebral cortex resulting in cognitive symptoms that start to appear. The identification of pathologic SYN by immunostaining in the post mortem brain is now the definitive pathological marker for PD.

Recent reports of SYN deposits in other organ systems, including the heart, gut, salivary glands, and skin, suggest that some of the non-motor manifestations of PD might be explained by the impact of SYN at these sites, mediated through the autonomic nervous system. For example, prodromal constipation might be caused by deposition of SYN in the autonomic neural network in the walls of the intestines that regulate intestinal motility. A gut-to-brain transmission of SYN along the pathway of the vagus nerve from its terminals in the gut to its origin in the brainstem has become a plausible explanation for prodromal constipation. Similarly, another hypothesis holds that prodromal loss of the sense of smell (hyposmia) may indicate a nasal portal of entry for an unknown environmental toxin that causes a pathologic conversion of normal SYN in nasal nerve endings, followed by its spread along the olfactory pathway to the brainstem.

**Cognitive Impairment and Dementia**

Cognitive impairment and dementia are remarkably common in PD, usually occurring late in the illness, but noticeable in some people in the earliest stages. Those with early onset dementia,
generally starting within a year of motor symptoms, have been classified as having a clinically distinct but related disorder known as dementia with Lewy bodies (DLB). There is ongoing debate among experts as to whether PD and DLB are truly different disorders or merely two points on the spectrum of a single disease.

As many as 80 percent of patients with PD will eventually develop dementia. It is currently impossible to predict which patients will become demented and who will not. The typical profile of cognitive impairment in PD is a decline in executive function (multitasking, decision making, and organizing) and visual-spatial perception, in contrast to Alzheimer’s disease (AD), where early loss of recent memory is the hallmark. As these two neurodegenerative disorders progress toward their end stages, the neuropsychiatric symptoms come to resemble one another.

The pathological basis of the dementia of PD (PDD) was once thought to be caused by co-existing but unrelated AD with its post-mortem finding of amyloid plaques and neurofibrillary tangles. However, newer evidence, accumulated since the discovery of SYN, shows that the pathology of both disorders is more complex. In most patients with PDD, SYN—spread widely throughout the cerebral cortex—is the predominant finding. In about a third of the cases, there is a mixture of SYN with plaques and tangles, and this combination of PD and AD pathologies accelerates the rate of clinical decline. New methods for imaging the brain’s molecular pathology during life are becoming available to improve diagnostic accuracy and to stratify patients by types of pathology (i.e., plaques, tangles, and SYN) for clinical trials of experimental drugs.

Treatment of cognitive impairment in PD is usually disappointing, although cognitive enhancing drugs on the market for treating AD occasionally help. Health care providers must also be aware that unrelated medical problems, such as infections, organ failure, and adverse effects of medications used to treat pain (particularly after a surgical procedure), insomnia, anxiety, and depression can destabilize cognition in any patient with PD.

Cognitive exercises (puzzles, games, etc.) have been highly promoted as a strategy to prevent cognitive decline in a variety of neurological disorders (including PD), although evidence to support their effectiveness is lacking. The picture is a little brighter for physical exercise, in that the positive
impact on cognition of regular aerobic workouts, even as little as 30 minutes of daily walking, is becoming more evident.

**Psychosis (Illusions, Hallucinations, and Delusions)**
Cognitive impairment predicts the emergence of psychosis in 50-60 percent of all patients with PD. It often begins with a misinterpretation of a true sensory experience, such as “seeing” the shape of a human body in a street lamp post, or “hearing” voices when water is running. A true hallucination is a perceived distortion of reality in the absence of a stimulus: visual hallucinations are the most common psychotic symptom in PD; auditory, olfactory, and tactile hallucinations are rare. “Presence” hallucinations—the false sense that someone is standing near—are a common, early manifestation of psychosis in PD.

Over time, hallucinations evolve into well-formed visions of people and animals, which are usually friendly, non-threatening and ultimately understood not to be real. However, when they advance to be perceived as real and disruptive to daily life, treatment becomes necessary. Delusions (false and fixed beliefs), usually persecutor in nature, can also be a prominent feature of PD psychosis and often accompany visual hallucinations. Common delusions include spousal infidelity, stolen money, intruders, or “others” plotting to do harm. Many patients retain insight that their delusions and hallucinations are not real. However, some cannot be dissuaded from an isolated, fixed delusion, even when thinking is otherwise lucid. Research has shown that psychosis, not impaired mobility, is the single greatest PD risk factor for nursing home placement and for caregiver burnout.

A real-life vignette from a movement disorders specialist illustrates the complex nature of typical chronic psychosis:

“I sat in the examination room with my patient and his wife—just the three of us—but he reported that several friends had joined us; an elderly woman and two small children playing on the floor. He realized in the office that the extra visitors were imaginary, but when he was at home alone without others to help him navigate reality, their presence was so real that he panicked about unwanted intruders.”

The probable cause of PD psychosis is a complex interaction of SYN pathology and an imbalance of the neurotransmitters: dopamine, acetylcholine, and serotonin sending excitatory and inhibitory
signals through the brain’s synapses. Any of the many anti-parkinson medications can induce psychosis, although the dopamine-agonist drugs used (which mimic dopamine) as second line agents are the biggest offenders, compared with the standard carbidopa/levodopa. Drug-induced psychosis tends to diminish when medications are reduced or discontinued but may not resolve completely—evidence that the underlying PD pathology alone can be responsible.

Treatment of hallucinations consists of a careful reduction of anti-parkinson medication (if tolerated without substantial worsening of the motor symptoms) and the addition, if necessary, of a hallucination-suppressing drug. Traditional antipsychotic medications work by blocking dopamine receptors, but since PD is a disease of dopamine deficiency, they pose an unacceptable risk of worsening motor symptoms. However, several, newer “atypical” antipsychotic medications that do not significantly impact the dopamine system can be used safely as off label therapy (Drugs that are used off-label are FDA-approved for a specific indication but can be prescribed by physicians for other indications.) In 2016, the FDA approved pimavanserin (Nuplazid) as the first and currently only drug for the specific treatment of PD psychosis, although confusion is listed as one of its side effects.

Mood Disorders

Depression, anxiety, and apathy frequently complicate the lives of patients with PD. In one survey, mood disorders were ranked the most troublesome of the non-motor symptoms. Depression is the most common, affecting 40-50 percent of people. Depression can also be a prodromal sign of PD.

Depression in PD is under-recognized, in part, because it can be masked by PD’s inherent psychomotor slowing, bradykinesia (rigidity), and mask-like facial expression. Furthermore, such depression symptoms as decreased appetite, difficulty with concentration, and disturbed sleep are commonly seen even in PD patients who are not depressed.

Anxiety

Anxiety commonly accompanies depression in PD, with generalized anxiety disorder and social phobia the most important subtypes. Feelings of depression, anxiety, and panic are also common in patients who are plagued by the “wearing off” phenomenon that occurs in more advanced stages of
illness: at the end of a dose of carbidopa/levodopa, re-emergence of severe motor deterioration can cause such feelings even with the realization that the next dose of medication will quickly restore benefit.

Apathy and Fatigue
Apathy (loss of motivation) and fatigue (chronic tiredness and easy exhaustion) are complaints that patients with PD frequently bring to their health care provider. Both can occur with or without depression. When no cause can be identified, it is usually considered without good evidence to be an unexplained feature of the underlying PD.

Sleep Disorders
Insomnia, excessive daytime sleepiness, restless leg syndrome (RLS), and Rapid Eye Movement sleep behavior disorder affect between 50-75 percent of patients with PD. The most common sleep disturbances are failure to fall asleep, sleep fragmentation (frequent awakening throughout the night), and early morning awakening.

There are many potential causes of frequent awakenings in PD, but the most common are increased need to urinate during the night because of diminished bladder capacity, difficulty turning in bed, leg cramps, vivid nightmares, and back pain. A flare of tremors during the night due to the prolonged interval between doses of antiparkinson medication may also contribute.

Restless leg syndrome—an uncontrollable urge to move the legs when at rest, associated with an unpleasant tingling sensation, occurring mainly at night and relieved by voluntarily changing position—is common in the general population, but occurs disproportionately in patients with PD. RLS is not a movement disorder but a deeply annoying sensory experience related to dopamine deficiency. Patients with PD often report RLS at night when the benefit of levodopa is wearing off. Proof of its relationship to dopamine lies in the excellent benefit achieved with the use of a low-dose dopamine agonist.

REM sleep behavior disorder (RBD), or dream enactment behavior, is an often dramatic non-motor feature of PD. Like prodromal depression, hyposmia, and constipation, RBD often predates the
onset of motor symptoms. It can occur as an “idiopathic” (without apparent cause) disorder, but over half of those so diagnosed go on later—sometimes years later—to develop classic motor signs of PD.

Dreaming occurs during the 3-4 brief REM stages of a typical 8-hour sleep cycle. In normal dreaming, a control center in the brainstem suppresses muscle activity and overt emotional expression that might occur in response to the content of a dream. In PD, pathology in this brain area disables this inhibition, so vivid dreaming can be associated with uninhibited yelling, thrashing, flailing, kicking, and punching. Some patients fall out of bed or hit their bed partners. The patient with RBD is asleep and unaware of dream-related havoc but tends to remember the content of the dream the next day.

Excessive daytime sleepiness (EDS) in PD may be a compensatory response to sleep deprivation. Frequent, long naps and difficult arousal from a nap or a night’s sleep are typical. In the more advanced stages of PD, EDS is frequently an ominous harbinger of worsening cognitive impairment.

**Autonomic Insufficiency**

The human nervous system has two divisions: central—the brain and spinal cord; and peripheral—the nerves that emanate from the spinal cord to mediate sensory and motor functions of the rest of the body. The autonomic nervous system (ANS) is a peripheral subdivision that regulates unconscious and involuntary functions such as heart rate, blood pressure, rate of breathing, digestion, and sexual arousal. Its malfunction, due to PD pathology, can cause a drop in blood pressure upon standing (orthostatic hypotension); constipation; excess sweating; urinary frequency and incontinence; and sexual dysfunction. Autonomic abnormalities in PD vary greatly among patients but can be a major source of disability.

**Impaired Sense of Smell**

Diminished or absent sense of smell, also known as hyposmia or anosmia, is another prodromal biomarker of PD, usually occurring years before the onset of motor PD symptoms. Patients may be unaware of or indifferent to the deficit. Simple “scratch and sniff” testing has become standard in research protocols designed to identify and study people at risk for developing PD. Olfactory testing
can also be used to differentiate PD from other parkinsonian disorders in which the sense of smell remains normal. Impaired olfaction is also a pre-clinical marker of AD.

**Pain**
Unexplained pain is common in individuals with PD. It can be episodic or constant, cramp-like, or diffuse, and is often attributed to the rigidity affecting the large muscles of arms and legs. Other causes include twisting or “dystonic” spasms of the feet, and the involuntary movements known as “dyskinesia” that result from an over-reaction to levodopa. Pain is such a universal phenomenon that non-PD causes, such as arthritis, inflammation, and other medical disorders should always be considered.

**Looking Forward**
The spectrum of non-motor symptoms in PD is extremely broad, reflecting the widespread nature of PD pathology. Consequently, management of each patient requires the skills of multiple health professionals working as a team in a centralized facility such as a Parkinson’s Disease and Movement Disorders Center. Such facilities are usually located in a major university-based medical complex and provide access to specialty trained neurologists, psychological counselors, psychiatrists, physical and occupational therapists, social workers, surgeons experienced in the most advanced interventions, and clinical researchers who offer access to clinical trials of experimental therapies.

The treatment of PD has advanced little from the introduction of levodopa 50 years ago, despite repeated out-of-the-box attempts to develop a new generation of innovative pharmaceuticals. Particularly disappointing is the failure of the pharmaceutical industry to exploit basic scientific discoveries of new molecular targets and genetic mutations with the potential to modify or arrest the neurodegenerative process underlying PD. Transplantation of embryonic cells into the basal ganglia held much promise as a potentially curative therapy, but several well-designed and executed clinical trials have shown no benefit whatsoever.

The best hope for a paradigm shift in managing PD is for breakthrough research to develop disease-modifying interventions for the prodromal phase of the disease. Here, identifiable genetic,
biochemical, and clinical biomarkers might light the way toward converting PD from a disabling progressive disorder to a benign chronic illness.

Financial Disclosures

Bios

Sarah Horn, M.D., is an Edmond J. Safra Fellow in Movement Disorders at the University of Pennsylvania, completing the second year of a two-year fellowship. She received her M.D. degree from the University of Texas in Houston in 2013, then became a resident in Neurology at the Beth Israel Deaconess Medical Center in the Harvard Medical System. Board-certified in neurology, Horn is a fully trained clinical specialist in movement disorders. Her research interests include comparative effectiveness of therapeutic interventions and clinical trials of experimental medications. A Texas native, she has accepted an offer to join the faculty of the University of Texas in San Antonio starting in the fall of 2019.

Howard Hurtig, M.D., is the Frank and Gwladys Elliott Professor of Neurology, Emeritus, at the Perelman School of Medicine, University of Pennsylvania. A native of Mississippi, his early education was at Tulane University. His post graduate training began at Cornell-New York Hospital in internal medicine followed by residency in Neurology at Penn. He joined the Penn Medical faculty in 1973, ascending to professor in 1987. He was named Chair of Neurology at Pennsylvania Hospital, a division of the University of Pennsylvania Health System, in 1997 and the Elliott Professor in 2006. In 1982, Hurtig and colleagues Matthew Stern, M.D., and nurse Gwyn Vernon founded the comprehensive Parkinson Disease and Movement Disorders Center at the University of Pennsylvania. He is a member of Penn Medicine’s Academy of Master Clinicians and has a research interest in the molecular pathology of Parkinson disease and related neurodegenerative disorders.