INTRODUCTION

Parkinson’s disease (PD) is a neurodegenerative disorder involving degeneration of dopaminergic neurons in the substantia nigra. It is the second most common neurodegenerative disorder following Alzheimer’s disease. Its etiology is unknown but is speculated to be a combination of genetic factors and environmental influences. Diagnosis of PD, especially early in the course of the disease, is not always easy. There is no biomarker or accepted diagnostic test for PD; the diagnosis is made clinically based on the four cardinal signs of PD: resting tremor, rigidity, bradykinesia, and postural instability. Several factors can confound the diagnosis including secondary forms of parkinsonism caused by stroke, tumor, toxins or medications, and neurodegenerative disorders (parkinsonian syndromes) that share some common features with PD. These include progressive supranuclear palsy, multisystem atrophy, corticobasal degeneration, and diffuse Lewy body disease. Once an accurate diagnosis is made, treatment and management of symptoms can begin. Following are three cases that illustrate different aspects of PD with an emphasis on diagnosis and treatment with current as well as emerging treatment options.

CASE 1

The patient is a 65-year-old, right-handed male presenting with a 10-year history of tremor. He had tremor involving both hands and head, which he felt had progressed in severity over time. The tremors interfered with eating, drinking from a cup, and shaving. He noted some slowness in his gait and difficulty getting in and out of a car. His handwriting was shaky and had become smaller over time. His grandfather and uncle had experienced similar tremors; his uncle had been diagnosed with essential tremor. The patient had not received any treatment for this tremor.

Notable in the patient’s past medical history were hypertension and gastroesophageal reflux disease. His medications included atenolol 25 mg QD for hypertension and metoclopramide 10 mg BID for gastroesophageal reflux. The latter condition was also managed with diet. The patient appeared to have a combination of both essential tremor and parkinsonian resting tremor. Slide 2 lists features of parkinsonian tremor and essential tremor. Resting tremor is characteristic of PD, occurring when the limb is at rest, and diminishes or disappears with activation of the limb.1 Resting tremor tends to respond to dopaminergic treatment. Postural tremor occurs while voluntarily maintaining a position against gravity, and can be seen in both PD and essential tremor. Intention tremor is the most common form of tremor in essential tremor. Intention tremor occurs with visually guided movements toward a target.2 There appears to be a possible relationship between essential tremor and PD. Tan and colleagues3 found an increased frequency of essential tremor in patients with PD compared to controls. Relatives of patients with PD have an increased risk of developing essential tremor, especially when relatives with PD experience younger age of onset and/or tremor-predominant PD.4 Louis and colleagues5 reported the presence of Lewy bodies, a common neuropathologic finding in PD, in the locus ceruleus. Yahr and colleagues6 reported the co-occurrence of essential tremor and PD in a large family who presented with essential tremor several years prior to the development of PD.6 Chaudhuri and colleagues7 suggested that asymmetrical postural tremor is a precursor to PD and not essential tremor. There are

SLIDE 2

Characteristics of Parkinsonian Tremor and Essential Tremor

<table>
<thead>
<tr>
<th>Tremor type</th>
<th>Parkinson’s Disease</th>
<th>Essential Tremor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Distribution</td>
<td>Asymmetrical at onset</td>
<td>Symmetrical</td>
</tr>
<tr>
<td>Arm/leg tremor</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Head tremor</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Voice tremor</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Hereditary</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Alcohol responsive</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Dopamine responsive</td>
<td>+</td>
<td>–</td>
</tr>
</tbody>
</table>

+=present; =absent.
different theories concerning this relationship: development of PD in cases of essential tremor is coincidental; it is an overlap between the two conditions, especially in those cases of shared features; or a subset of those with essential tremor may progress to the development of PD. Regardless of the nature of this relationship, patients may present with tremors of both disorders. The following can be helpful in distinguishing the two disorders: tremor, rigidity, and bradykinesia tend to have an asymmetric onset in PD, which distinguishes it from essential tremor. An element of rigidity can also be seen in essential tremor, though this is not a prominent feature. Alcohol responsiveness and family history are common elements of essential tremor that distinguish it from PD. Parkinson’s tremors tend to respond to dopaminergic medications, whereas essential tremor tends to respond to beta blockers and primidone. Both Parkinson’s tremor and essential tremor can respond to beta blocker treatment.

Another issue in this case is possible secondary parkinsonism. This patient was also taking metoclopramide, a neuroleptic. In addition to tardive dyskinesia, neuroleptics can cause parkinsonism. Other common drugs that can cause parkinsonism are included in Slide 3. A feature of drug-induced parkinsonism is that the disease state generally recovers once the offending agent has been discontinued. Recovery time can be prolonged, lasting weeks to months. Other common causes of secondary parkinsonism include structural abnormalities, such as stroke, hemorrhage, or tumor involving the basal ganglia, toxins, and degenerative diseases. Slide 4 lists the more common causes of secondary parkinsonism. In most cases, a careful history and physical exam, along with a magnetic resonance imaging of the brain (when structural abnormalities are suspected), can eliminate secondary parkinsonism from the differential diagnosis.

### Treatment
Following the initial evaluation, the patient discontinued metoclopramide, which had not changed the tremor. The patient was then started on a low dose of primadone to help with the essential tremor, which appeared to be more troublesome. Adjustment of atenolol was not possible due to the patient’s low blood pressure. At follow-up evaluation one month later, the essential tremor was improved. The patient did not have excessive sedation as a result of primadone and was able to eat with a spoon and drink from a cup. He continued to have resting tremor involving the right hand. At the one-year follow up, resting tremor was more apparent. The patient tended to drag the right leg slightly on gait testing.

As he appeared to show more signs of PD, the patient began treatment with a monoamine oxidase (MAO) type-B inhibitor. Rasagiline 0.5 mg QD was started, and then increased to 1.0 mg QD 2 weeks later. The patient appeared to feel improved with this medication, which helped his symptoms.

Rasagline, an MAO-B inhibitor, is a specific inhibitor of the enzyme monoamine oxidase, which is involved in the breakdown of dopamine. MAO-B inhibitors reduce the destruction of dopamine, thereby increasing endogenous dopamine. MAO-B inhibitors appear also to have another beneficial effect independent of this action. They are thought to have anti-oxidant properties and may have disease-modifying effects, as shown with rasagline at 1 mg QD in a recent double-blind study. The typical dosage of rasagline is 1 mg daily. Selegiline, another MAO-B inhibitor, is dosed at 5 mg BID. The following medications are contraindicated with rasagline: meperidine, tramadol, methadone, propoxyphene, dextromethorphan, mirtazapine, cyclobenzaprine, and St. John’s wort. Although rasagline is selective for MAO-B, the Food and Drug Administration recommends a low-tyramine diet to prevent the increase in blood pressure that can be seen with non-selective MAO inhibitors (such as phenelzine and tranylcypromine). MAO-B selective inhibitors can be used in combination with dopamine agonists and levodopa.

In addition to the initial use of an MAO-B inhibitor, either a dopamine agonist or levodopa can be used. The American Academy of Neurology practice parameters do not distinguish between dopamine agonists and levodopa.

### SLIDE 3
Common Drugs Resulting in Parkinsonism

<table>
<thead>
<tr>
<th>Neuroleptics:</th>
<th>Haloperidol</th>
<th>Fluphenazine</th>
<th>Chlorpromazine</th>
<th>Thioridazine</th>
<th>Olanzapine</th>
</tr>
</thead>
<tbody>
<tr>
<td>Antiemetics:</td>
<td>Promethazine</td>
<td>Prochlorperazine</td>
<td></td>
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<tr>
<td>Gastrointestinal motility agents:</td>
<td>Metoclopramide</td>
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<tr>
<td>Reserpine</td>
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<tr>
<td>Tetrabenazine</td>
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<tr>
<td>Cinnarizine</td>
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<td></td>
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<tr>
<td>Flunarizine</td>
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</tbody>
</table>

### SLIDE 4
Common Causes of Secondary Parkinsonism

<table>
<thead>
<tr>
<th>Structural Causes</th>
<th>Stroke or multiple lacunae in basal ganglia</th>
<th>Vascular malformations in basal ganglia</th>
<th>Giant aneurysm in internal carotid and middle cerebral artery</th>
<th>Normal pressure hydrocephalus</th>
<th>Tumor, abscesses in basal ganglia</th>
<th>Calcification of basal ganglia</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trauma</td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug induced</td>
<td>See Slide 3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Toxin induced</td>
<td>MPTP</td>
<td>Carbon monoxide</td>
<td>Manganese</td>
<td>Cyanide</td>
<td>Mercury</td>
<td>Methanol</td>
</tr>
<tr>
<td>Family or hereditary parkinsonism</td>
<td>Progressive supranuclear palsy</td>
<td>Multiple system atrophy</td>
<td>Corticobasal degeneration</td>
<td>Diffuse Lewy body dementia</td>
<td>Hallervorden-Spatz disease</td>
<td>Neuroacanthocytosis</td>
</tr>
</tbody>
</table>
as first-line agents. Medications should be tailored to the individual patient, his or her tolerance to the medications, and the medications’ beneficial effects. The goal of therapy is to best manage the symptoms with the fewest side effects for as long as possible.

Dopamine agonists stimulate the postsynaptic receptors, effectively bypassing dopamine. They are effective in alleviating symptoms and in delaying the need for levodopa. Ropinirole and pramipexole are the two dopamine agonists commonly used to treat Parkinson’s symptoms. Ropinirole is available in an extended-release formulation as well as an immediate-release form. Dosage of ropinirole ranges from 0.25 mg TID to 8 mg TID, and the extended release form ranges from 2 mg QD to 24 mg QD. Pramipexole dosage ranges from 0.125 mg TID to 1.5 mg TID. Sedation is one of the known side effects from dopamine agonist use and can induce sleep attacks during which the patient falls asleep suddenly. Patients with sleep apnea and excessive sedation are not candidates for dopamine agonist use. Impulse control disorders, including pathological gambling, shopping, and sex, have been associated with dopamine agonist use in a subset of patients. Patients should be monitored for signs of compulsive behavior, which may warrant discontinuation or switching of dopamine agonists. Dopamine agonists can be used in combination with MAO inhibitors or levodopa.

Carbidopa/levodopa continues to be the gold standard of treatment of PD. Levodopa is absorbed through the duodenum and transported across the blood-brain barrier, where it is converted into dopamine and taken up by the presynaptic dopaminergic neuron. The initial maintenance dosage of carbidopa/levodopa is titrated to 25/100 TID and is further increased, over time, according to need. It has a short half-life of 1.5–2 hours in the serum, and its effectiveness is dependent on the number of functional presynaptic neurons. In time the dosage interval requirement grows shorter. Carbidopa/levodopa can be used alone or in combination with other available medications. Long-term side effects include on/off motor fluctuations and dyskinesias.

**CASE 2**

The patient is a 57-year-old, right-handed female who began to notice tremor in her right arm ~1 year ago, as well as rigidity involving the right side and bradykinesia. She was observed talking and moving about in her sleep. She was diagnosed with PD and was started initially on pramipexole, 0.25 mg TID. She responded well to the medication.

Within the next 6 months, her symptoms progressed; tremor and rigidity began to affect the left side. Medications were adjusted, including an increase of carbidopa/levodopa. The patient again responded somewhat to the medication, but some symptoms were less well controlled. Her balance was affected, and she started to fall frequently. Additional medications were added, including pramipexole and rasagiline, with questionable benefit. At times the patient began to become lightheaded upon standing. She was brought to the clinic after losing consciousness at a grocery store. Her blood pressure was 120/89 sitting and 100/80 standing, with pulse of 72 and 76 respectively. It was thought that her medications were affecting her blood pressure; her antihypertensive agent was consequently discontinued. Eventually pramipexole was reduced and discontinued for the same reason.

The patient sought consultation for deep brain stimulation (DBS). Her medications included carbidopa/levodopa CR 50/200 five times daily, carbidopa/levodopa 25/100 five times daily, entacapone 200 mg five times daily, and rasagiline 1 mg daily. On examination, the patient’s blood pressure was 129/80 sitting and 101/77 standing, with a pulse of 76 and 68 respectively. She had a hoarse voice with somewhat dysarthric speech, as well as a rigid tremor involving both upper extremities and her right lower extremity, with marked rigidity of the neck and both lower extremities. A lesser amount of rigidity was seen in her right upper extremity. Rapid alternating movements were bradykinetic and incomplete. She was barely able to perform heel taps on the right. She was unable to stand without pushing herself up with her arms. On examination of gait, she had a stooped posture with a wide-based stance and shortened stride. Full test was positive without recovery. Based upon her history and examination findings, she was counseled against DBS surgery.

Case 2 illustrates a patient with a parkinsonian syndrome, most likely multiple system atrophy with autonomic nervous system involvement, also known as Shy-Drager Syndrome. Patients with this disorder often present with signs of PD and may even respond to similar medications early in the course of the disease. Several features distinguish parkinsonian syndromes from PD, including early falls, poor response to levodopa, symmetry of motor manifestations, lack of tremor, and early autonomic dysfunction. The latter includes symptomatic postural hypotension, urinary urge incontinence, fecal incontinence, urinary retention requiring catheterization, and persistent erectile dysfunction. There is no specific treatment for multiple system atrophy or other parkinsonian disorder. Palliative care remains the rule at present.

Rapid eye movement (REM) behavior disorder (RBD) is a sleep disorder in which the patient moves during the REM stage of sleep. RBD is commonly seen in the elderly patients with PD and other degenerative disorders. RBD in combination with a reduced response to medication and orthostatic hypotension is suggestive of multiple system atrophy.

**CASE 3**

The patient is a 50-year-old, right-handed male who began to notice tremor in his right arm ~10 years ago. Six months later he also reported tremor in his left arm. The tremor occurred at rest and disappeared with activity. The patient also noted that his handwriting worsened and his lettering was smaller. He walked increasingly more slowly and developed slowness in his daily activities. The patient was diagnosed with PD, and was started initially on pramipexole, to which he responded well for ~1 year. The effect wore off; consequently, carbidopa/levodopa and entacapone were added. He responded well to these medications.

The patient developed an intense interest in collecting gold coins, which he purchased over the Internet. He spent tens of thousands of dollars per month on this hobby. After his wife convinced the coin dealer to stop selling to the patient, the patient began to gamble online, amassing $300,000 in losses over a few months. His credit card was revoked, and his wife filed for divorce. Pramipexole was discontinued, and the patient was treated with carbidopa/levodopa and entacapone only. The patient was constantly short of his medication before refills. He felt that he could not tolerate the onset of off time and had a tendency to take more medication than prescribed. He explained that, as a former fighter pilot, he was accustomed to high adrenaline, and the carbidopa/levodopa provided the “rush” he needed. He spent excessive amounts of time cleaning and organizing his room, only to create bigger messes with his reorganization. He also

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constantly upgraded and repaired his computer, even when it functioned properly, sometimes breaking it in the process. After repeated dose adjustment of carbidopa/levodopa, the patient decided to apply for DBS. After DBS and with low-dose carbidopa/levodopa, the patient is doing well.

Case 3 illustrates the impulsive behavior seen in some PD patients taking dopaminergic medication. In PD, there is increasing evidence for disorders in the impulsive-compulsive spectrum. These disorders could either be the consequence of the disease or of the pharmacologic management. They include dopamine deficiency syndrome (with immediate reward-seeking behavior), dopamine dependency syndrome (with addictive behavior), dopamine dysregulation syndrome (with both addictive behavior and stereotyped behavior), and impulse control disorders (such as pathological gambling, compulsive shopping, binge eating, and hypersexuality). These disorders are especially seen in PD patients with young age of onset, those receiving higher doses of antiparkinsonian drugs, those who have pre-existing or current depression, those with pre-existing recreational drug or alcohol use, and those with high novelty-seeking personality traits. They can occur in up to 14% of PD patients on dopamine agonists. In this patient, compulsive shopping and gambling were evidence of an impulse control disorder.

The patient also had symptoms of dopamine dependency syndrome. Dopamine dependency syndrome is thought to be caused by dopamine replacement therapy in the PD-related striatal dopamine deficiency. The patient, in an effort to control dysphoric “withdrawal” symptoms in the off state, took a quantity of levodopa far beyond that required to treat his motor disabilities. Such patients demand rapid drug escalation, requesting increased levodopa despite the eventual emergence of severe drug-induced motor complications and harmful behavioral consequences. They often request prescription refills more frequently, and may explain that depression or sadness leads them to take more medication. They prefer excessive dyskinesia despite concerns of family members. In the treatment of dopamine dependency syndrome, psychosocial strategies are needed, as is active involvement of the patient’s family members together with gradual, carefully supervised reduction of dopaminergic medications. Quetiapine has also been recommended.

Another side effect of Parkinson’s therapy is punding behavior, characterized as “compulsive hobbyism.” These patients have an intense, inappropriate, and unproductive fascination with common objects, and enact repetitive, meaningless movements such as endless computer use, cleaning and tidying, gardening, collecting, repairing and/or dismantling (eg, watches and radios) and sorting of common objects (eg, rocks). In Case Study 3, punding was expressed as constant cleaning and computer repairing. Due to physicians’ lack of awareness and patients’ reluctance to report embarrassing symptoms, punding symptoms are under-recognized and under-reported with serious psychosocial consequences. In some cases, punding is associated with hypersexuality, pathological gambling, or dyskinesia. O’Sullivan and colleagues have recommended a suggested screening questionnaire for punding to screen for these symptoms. As it is suspected that punding is caused by striatal dopamine receptor hypersensitivity, treatment strategies aim to desensitize these receptors through continuous dopamine receptor stimulation. There is no identifiable pattern to the dopamine receptor stimulation profile of the medications used by the punders compared with the nonpunders. Recently, amantadine has been reported to reverse disabling punding in a PD patient, without aggravating motor parkinsonism.

The goal in treating this patient is to avoid dose fluctuations in the dopaminergic therapy, if possible. Recently, a few innovative treatments have been introduced such as DBS, dopamine agonist patches, and enteral levodopa/carbidopa infusion. Motor fluctuations can especially be reduced by intraduodenal infusion of levodopa. Patients experienced improvement in dyskinesia after the introduction of such continuous treatment, with the mean daily levodopa consumption slightly reduced with infusion compared to oral therapy. DBS in the subthalamic nucleus also has been reported to improve disabling motor fluctuations, dyskinesia, and dopamine dysregulation syndrome. It also abolished the addiction to dopaminergic treatment in two patients.

CONCLUSION

The diagnosis of Parkinson’s disease presents many challenges. Patients may present with confusing tremors or may develop additional symptoms outside of those usually recognized in PD despite a good early response to dopaminergic medication. Early treatment of PD is also important. In the last decade, the understanding and therapeutic management options for PD have increased significantly. We have learned that PD is not just a motor disorder but also has non-motor complications. These cases illustrate some subtle and potentially confusing symptoms that careful physicians need to understand in order to optimize treatment.

REFERENCES