ABSTRACT

Parkinson’s disease (PD) is diagnosed primarily with a “low-tech” approach of listening (patient history) and observing (neurological examination), and in some cases watchful waiting over several years. Diagnosing idiopathic PD can be challenging due to its insidious onset, lack of pathognomonic signs or symptoms, and especially the lack of laboratory or imaging tests that confirm the diagnosis (a disease “marker”). Although historically considered to be a pure movement disorder, PD is now being recognized as a neuropsychiatric disorder with many non-motor symptoms that can predate motor symptoms and can be equally disabling. Depression is one of the most common non-motor PD symptoms. Early in the disease, there are many non-medical therapies that help to improve motor function, independence, and quality of life. Using extracts from an interview with a patient, who describes her early signs and symptoms and the diagnostic process from her point of view, this article discusses early diagnosis of PD, particularly with regard to patient history and non-motor features of PD. Currently available diagnostic tools, non-medical treatments of PD, and PD pathology will also be discussed.

INTRODUCTION

Diagnosing idiopathic Parkinson’s disease (PD) can be challenging, due to its insidious onset and lack of pathognomonic signs or symptoms, but mostly because there is no laboratory or imaging test that confirms the diagnosis. As a result, making a diagnosis of PD frequently requires a period of watchful waiting. For some patients, it may be several years until the physician can diagnose PD with reasonable certainty. In other cases, an early diagnosis of PD has to be revised later on, when atypical features emerge to suggest other forms of parkinsonism, for example multiple system atrophy (MSA) or progressive supranuclear palsy (PSP).

Using extracts from an interview with a patient, who describes her early signs and symptoms and the diagnostic process from her point of view, this article will discuss early diagnosis of PD, particularly with regard to patient history and non-motor features of PD. Currently available diagnostic tools, non-medical treatments of PD, and PD pathology will also be discussed.

CASE STUDY: DW

DW is a 45-year-old woman who initially presented to a neurologist after 2 years of difficulty with dexterity and a feeling of heaviness in her left hand. She also described herself as being clumsy and unable to perform necessary activities.

PATIENT INTERVIEW

I first noticed a problem about 5 or 6 years ago. There was a slowness on my left side when I exercised.

*Based on a presentation given by Dr Verhagen Metman at a symposium held in Salt Lake City, Utah, on September 19, 2008.
†Associate Professor, Department of Neurological Sciences, Movement Disorders Section, Rush University Medical Center, Chicago, Illinois.

Address correspondence to: Leo Verhagen Metman, MD, PhD, 1725 W Harrison Street, Suite 755, Chicago, IL 60612. E-mail: lverhage@rush.edu.

*DW is a patient of Cynthia L. Comella, MD, Professor, Department of Neurological Sciences, Movement Disorders Section, Rush University Medical Center, Chicago, IL. The extracts included in this article are from an interview between Dr Comella and DW earlier this year.
When I lifted weights, my left and right sides were not symmetrical, but I just attributed it to being out of shape. When I was running, I noticed that my left side felt heavy and my left foot was clomping more on the pavement. I attributed that to being out of shape as well. That continued for several months but I did not mention it to anyone. During one jog, however, I fell and I did not know why—there was no obvious obstacle in my path. It was a hard fall; I broke my finger. My husband had been noticing the changes in me, and he insisted then that I see a doctor.

I went to my primary care doctor, who also noticed the slowness on my left side. He did not give any indication as to what he thought might be the problem but referred me to a neurologist. Those were the only symptoms I was having, so the neurologist did a “watch and wait,” thinking it might be multiple sclerosis (MS).

THE PATHOLOGY OF PD

At this point, a diagnostic test for PD would have been helpful to both the treating physician and the patient (DW). Although the field of neuropathology does not provide diagnostic answers for PD during life, recent advances in this domain are at least helping us understand some of the early symptoms of PD and thus aid in the diagnostic process. The pathologic hallmarks of PD are classically thought to be: (a) degeneration of dopamine-producing neurons in the substantia nigra; and (b) Lewy bodies in the cytoplasm of remaining dopaminergic neurons. A major constituent of the Lewy body is the protein α-synuclein. New immunocytochemistry techniques exploit the immune response to α-synuclein to detect the presence of Lewy bodies with improved accuracy.

In a recent landmark study, the German pathologist Heiko Braak and colleagues used this technique to examine brains in a cross-sectional study of more than 400 non-selected autopsy cases. They demonstrated that Lewy body pathology is present in many regions of the brain (and even outside the brain) long before the substantia nigra is affected. In addition, they found that the formation of Lewy body pathology occurs in a caudo-rostral trajectory—that is, it begins in the medulla and ascends to the pons, midbrain, and mesocortex, and ultimately reaches the cerebral cortex. Based on this distinctive temporospatial distribution of Lewy bodies, Braak recognized 6 neuropathologic stages in PD (Figure).1-3 Although not all patients with PD progress at the same pace, the pathologic changes usually occur in the same sequence.

PATIENT INTERVIEW (CONTINUED)

The neurologist I saw was an MS specialist. By that time, I had started to develop tremor in my left leg and the toes on my left foot started to curl. I also noticed slightly less movement on the left side of my face; it really became apparent when I smiled, or tried to smile. I wasn’t in the doctor’s office for 30 minutes before he said, “This doesn’t look like MS. It looks more like Parkinson’s disease [PD].” That was the first time that I had heard anyone mention PD. When I heard him say that, part of me was
intrigued, because I had spent so long trying to adjust to being an MS patient. Ultimately, I simply wanted to know what I had, because he did not say, “You have PD.” He said, “It looks like PD. It’s definitely not MS.” It seemed that he was ruling out one disorder, but not necessarily ruling in the other one.

When I was learning about MS, I knew I didn’t have all of the symptoms, but when I started to read and learn about PD, I felt like I was reading about myself, especially young-onset PD. I read about the slowness of movement, the problems with balance, the asymmetry of the symptoms, the foot dystonia (what I call my “curly toes”). It became clear to me that I had PD based on what I read, even before I was officially diagnosed by a movement disorder neurologist.

TOOLS FOR DIAGNOSING PD

As DW was able to recognize, the signs and symptoms at presentation are critical to diagnosing PD (see www.JHASIM.com/PD2008/Verhagen for DW’s description of her signs and symptoms). For the physician, to make an initial diagnosis of idiopathic PD, the essential tools remain the patient history and physical examination. Although ancillary tests, including neuroimaging, genetic testing, and other laboratory tests, occasionally can provide useful information, they are used mostly to exclude forms of parkinsonism other than idiopathic PD. Magnetic resonance imaging scans are normal in idiopathic PD but may show abnormalities when parkinsonism is due to MSA, PSP, or vascular disease. Positron emission tomography and single photon emission computed tomography are currently used for research purposes only, at least in the United States, and as such are employed to obtain a quantitative measure of an individual’s dopaminergic system over time, rather than to make a diagnosis. Midbrain ultrasound is being developed mostly in Europe but is not yet sensitive enough to be used in clinical practice.

Olfactory disturbances are often seen early in PD, in line with Braak’s hypothesis, and smell tests are abnormal in most patients with PD. However, olfactory dysfunction is also seen in other degenerative disorders, including MSA, and therefore a smell test lacks specificity to be diagnostic for PD. Also, not every patient with PD develops anosmia early on. Even though a good response to levodopa is a key feature of idiopathic PD, a “levodopa challenge” is not a useful diagnostic tool early in the disease because many patients do not respond dramatically when first exposed. Levodopa response of tremor is particularly variable. Genetic testing is only used in rare cases, because the results currently do not affect disease management.

Aspects of the patient history that suggest PD include gradual onset and steady progression (as opposed to stepwise progression, which may suggest vascular events). The United Kingdom Parkinson’s Disease Society (UKPDS) Brain Bank (BB) has published Diagnostic Criteria that are widely accepted and used for diagnosing PD in clinical practice and for research purposes. According to the UKPDS BB criteria for PD, signs must include bradykinesia and at least 1 of the following: muscular rigidity, rest tremor, or postural instability. In addition, patients should not have any atypical features, such as early memory loss, early hallucinations, severe dysautonomia, cerebellar signs, or supranuclear gaze palsy. Finally, a list of supportive criteria that increase the probability of idiopathic PD is included, such as asymmetric onset, maintained asymmetry over time, and response to levodopa.

Signs and symptoms that will lead the clinician to diagnosing PD include slow, clumsy movements, small handwriting, decreased facial expression (the patient is described as appearing mad or depressed), decreased arm swing, especially without loss of strength, stooped posture, toe curling (as described by this patient, DW), turning in of the foot, cramps, and stiffness, especially in the shoulder. In fact, early PD is often misdiagnosed as a rotator cuff injury, with some patients undergoing surgery for a “frozen shoulder.”

Several atypical features that suggest one is dealing with something other than idiopathic PD are listed in Table 1.

PATIENT INTERVIEW (CONTINUED)

I don’t think that the other PD symptoms have gotten worse. I ask people closest to me if they notice any changes, because I may not notice some of them [these changes], but they do. For example, at night when I’m tired or in the morning when I wake up, I get an “owl face,” where my eyes get very big. That’s what my family notices.

I have been taking fluoxetine (20 mg) for the last 10 years—prior to being diagnosed with PD. Looking back, I think the depression was probably one of the
first symptoms of PD.

I'm not taking any medications for the PD. For me, I'll start a medication when my quality of life becomes so affected that I don't think I'd want to live that way.

**NON-MOTOR FEATURES OF PD**

Historically, PD has been considered to be primarily a motor disorder because its cardinal motor features are often so dramatic that non-motor issues have traditionally been overshadowed. However, we are now realizing that PD is actually a neuropsychiatric disease, with depression and anxiety occurring throughout the disease course and cognitive impairment and psychosis causing prominent disability later in the disease. We learn from DW that depression may have been a first symptom of PD for her.

Mild-to-moderate depression occurs in approximately 30% of patients with PD, and can precede the motor symptoms, as we see in this case study. Depression is often associated with anxiety, but anxiety by itself occurs in a large number of patients with PD as well. Rapid eye movement sleep behavior disorder (RBD) also can precede the onset of motor symptoms by several years. Interestingly, the neuroanatomical substrates of both depression (raphe nuclei) and RBD (pedunculopontine nucleus) are both localized to the brain stem. Therefore, observations that both depression and RBD precede the onset of PD are consistent with the caudo-rostral gradient of Lewy pathology proposed by Braak.

Signs of autonomic dysfunction include erectile dysfunction, low blood pressure or mild orthostatic hypotension, and urinary frequency or urgency. Of note, early onset severe orthostatic hypotension and urinary incontinence are not seen in idiopathic PD but suggest MSA. Cognitive impairment is not part of early PD. However, a recent study suggests that the majority of patients with PD will have cognitive impairment 20 years after disease onset. Drug-induced hallucinations and delusions also occur late in the disease, often associated with cognitive dysfunction. If psychotic features occur early in the disease without any or with low-dose dopaminergic agents, then a diagnosis of Lewy body dementia should be considered.

There are several other non-motor features that are receiving increased attention. As mentioned earlier, loss of smell—first reported in the literature more than 25 years ago in association with PD—is now recognized as one of the early signs of PD and a formal smell test is being developed to help diagnose PD earlier. Recent studies suggest olfactory dysfunction (anosmia or hyposmia) occurs in 42% to 65% of patients with PD, again consistent with our new understanding of the neuropathology of PD.

**PATIENT INTERVIEW (CONTINUED)**

When I first received the diagnosis of PD, I was devastated. But, I knew I would have to be involved in my treatment. I set out to determine what kind of fitness program I would need, how I would get the support I would need to eat healthy and to be healthy. I developed a mantra, that I have to keep moving. I kept an image in my head of what type of grandmother I wanted to be. Now, 1 year later, I'm 25 pounds lighter; I'm much stronger; my balance is better; my attitude is better; my depression is better. All of those things are better because of the initial encouragement to exercise, though I couldn't exercise very much at all at first.

### Table 1. Features Suggestive of Atypical Parkinsonism and Other Disorders They Suggest

<table>
<thead>
<tr>
<th>Atypical Feature</th>
<th>Suggested Causative Disorder</th>
</tr>
</thead>
<tbody>
<tr>
<td>Early cognitive impairment</td>
<td>Lewy body dementia, NPH</td>
</tr>
<tr>
<td>Early hallucinations</td>
<td>Lewy body dementia</td>
</tr>
<tr>
<td>Rapidly progressive course</td>
<td>MSA, PSP, CBD</td>
</tr>
<tr>
<td>Severe dysautonomia</td>
<td>MSA</td>
</tr>
<tr>
<td>Cerebellar signs</td>
<td>Ataxia, MSA</td>
</tr>
<tr>
<td>Supranuclear gaze palsy</td>
<td>PSP</td>
</tr>
<tr>
<td>Babinski sign</td>
<td>MSA, vascular parkinsonism</td>
</tr>
<tr>
<td>Strictly unilateral after 3 years</td>
<td>Stroke, CBD</td>
</tr>
<tr>
<td>Neuroleptic treatment</td>
<td>Drug-induced parkinsonism</td>
</tr>
<tr>
<td>Stepwise progression</td>
<td>Vascular parkinsonism</td>
</tr>
<tr>
<td>Lower body parkinsonism (including freezing of gait)</td>
<td>Vascular parkinsonism</td>
</tr>
<tr>
<td>Early urinary incontinence</td>
<td>MSA, NPH</td>
</tr>
<tr>
<td>Early postural hypotension</td>
<td>MSA</td>
</tr>
<tr>
<td>Early postural instability</td>
<td>PSP, MSA</td>
</tr>
<tr>
<td>Early falling</td>
<td>PSP, MSA</td>
</tr>
<tr>
<td>Unilateral apraxia, myoclonus, dystonia, cortical sensory loss</td>
<td>CBD</td>
</tr>
</tbody>
</table>

CBD = corticobasal degeneration; MSA = multiple system atrophy; NPH = normal pressure hydrocephalus; PSP = progressive supranuclear palsy.
Once I was able to build up some strength, exercise has made a tremendous difference.

The tremor still bothers me, but other people don't seem to notice it or comment on it. To them, it simply looks like I am a bit nervous. It has not interfered with my work. [DW is a preschool teacher.] I've been able to maintain full activity.

NON-MEDICAL THERAPIES FOR PD

Non-medical therapies are an essential component of the treatment plan for PD at any stage, but often represent the main treatment modality in early disease. The main goal with these therapies is to improve quality of life for the patient. There are no data to show that non-medical therapies affect disease progression, but studies have shown that non-medical therapies can help patients remain active, functioning, and independent for as long as possible.5-18

Non-medical therapies that can be explored are listed in Table 2. As we see with DW, exercise can be extremely beneficial, for several reasons. Exercise simply makes patients feel better, especially if they are able to lose some weight in the process, and exercise is known to help alleviate depressive symptoms. The American Academy of Neurology notes that exercise may be helpful in improving motor function for patients with PD.7 Specific types of exercise, such as pilates, yoga, and balance training, help with stabilizing the core muscles, which improves balance.10,11,14,15

Dance therapy (ie, learning to dance the tango, in lessons designed specifically for patients with PD) has been very popular among our patients, and a preliminary, randomized study comparing tango classes with exercise classes in 19 patients with PD showed that tango classes offered significant improvements in motor functioning and balance compared with exercise, which already has established benefits.19

Of note, some preclinical studies of exercise in other neurologic disorders suggest that exercise may be able to attenuate disease progression, but the mechanism by which this putative effect occurs remains speculative.

PATIENT INTERVIEW (CONTINUED)

I continue to exercise 4 or 5 days per week, for an hour to 90 minutes per day. I do strength training and cardiovascular exercises. Core strengthening has helped me tremendously; it's made a remarkable difference in my balance, because I had been stumbling a lot. My “curly toes” are the only painful part of the PD. If I become anxious, it can trigger the tremor in my left leg; my foot will cramp and my toes will curl so hard that the muscles in the top of my foot hurt. I can relieve it by removing my shoe and stretching my foot. But, it's not so painful that I need any kind of medical treatment for it, at least not right now.

My husband has been very supportive but it's taken him awhile to adjust; it's a process. Each time I feel another change in my body, it reminds me of the disease and I think, how dare I forget that I have this disease. I shouldn't have to think about how I walk, so the unfairness of the disease sometimes gets to me. But, I move past it. I just keep moving.

CONCLUSIONS

Although we are making great strides in the science of neurology, PD continues to be diagnosed primarily with a thorough patient history and neurologic examination. Laboratory tests and neuroimaging may be helpful to confirm the diagnosis or exclude other possible causes of parkinsonism, but for most patients, PD
is diagnosed with a “low-tech” approach of listening and observing. The UKPDS BB diagnostic criteria are widely used in clinical and research settings.

Parkinson’s disease pathology is now known to start in the lower brain stem and ascend rostrally to the dopaminergic pathways of the midbrain and beyond to the neocortex, in a predictable, temporospatial pattern. This process may occur at different rates in different patients with PD, but takes essentially the same route, providing an attractive explanation for symptoms that precede motor dysfunction.

Parkinson’s disease is no longer considered only a movement disorder; it is a neuropsychiatric disorder with many non-motor symptoms that can be as or more debilitating than the motor symptoms. Developing in parallel with this broadening view of the disease is the recognition that we need to widen our therapeutic arsenal by not only focusing on medical treatment of motor symptoms, but also including non-medical therapies. Exercise is one of the most useful non-medical therapies for patients with PD. Exercise can improve strength and balance, help with weight management, alleviate depression, and improve quality of life.

Through their responses during a clinic visit, patients will tell us what we need to know to diagnose PD and the treatments that work best for the individual patient.

REFERENCES