

There Is No Parkinson Disease

William J. Weiner, MD

The term *Parkinson disease* defines a specific clinical condition characterized by a typical history and characteristic signs. This review examines the historical evolution of the concept of Parkinson disease and how the misunderstanding of Parkinson disease may be hindering clinical research trials. It is proposed that this syndrome be called *Parkinson diseases* or *parkinsonism type 1 through infinity*. *Arch Neurol.* 2008;65(6):705-708

Battles over the nosologic classification of syndromes in medicine can often reach the intensity of religious debates. The term *Parkinson disease* requires rethinking, particularly in light of recent genetic advances. The definition of Parkinson disease has always been confusing, and I hope to convince the reader that there is no single Parkinson disease and that there never has been.

Neurologists agree that parkinsonism is a syndrome in which resting tremor, bradykinesia, cogwheel rigidity, and impaired postural reflexes are the predominant signs. The commonly accepted diagnostic criteria for Parkinson disease include parkinsonism with an asymmetrical insidious onset and a progressive course. Levodopa treatment responsiveness is often considered a diagnostic criterion. No recent history of antidopaminergic drug use and no atypical neurologic signs, such as saccadic eye movement abnormalities, early severe orthostatic hypotension, or symmetrical onset, should be present.¹⁻⁴ Neurologists believe that if they follow these guidelines, greater than 90% accuracy in diagnosis can be achieved, using the autopsy as the gold standard.⁵ However, what exactly is the clinical syndrome being diagnosed?

HISTORY

How did this syndrome come to be called Parkinson disease? James Parkinson de-

scribed 6 patients with supposedly heretofore unreported findings and designated the syndrome the *shaking palsy* or *paralysis agitans*.⁶ Careful reading of the 1817 essay raises considerable doubt about the “diagnosis” in 3 of the 6 patients. One patient has features of parkinsonism and orthostatic tremor, 1 patient has bilateral arm tremor of 5 years’ duration and no other motor symptoms, and 1 patient has only a gait abnormality. Three of the 6 patients are described as “casually met in the street or seen at a distance.” In none of the 6 patients is an examination described. More than half of the essay is devoted to speculation on etiology, pathologic anatomy, and cures. The monograph does contain astute descriptions of the gradual onset of asymmetrical symptoms, flexion posture, gait impairment, propulsion, sleep disturbance, constipation, speech dysfunction, and drooling.

Charcot paid tribute to Parkinson as the first to describe this disease,^{7,8} but he was dissatisfied with the names *shaking palsy* and *paralysis agitans* because there is no paralysis and because tremor is not always present. He thought that this syndrome would be better named *Parkinson disease*. Was Parkinson actually the first person to describe these motor signs? The syndrome is so distinctive that it is hard to believe that physicians before 1817 had never noticed it. Consider the following quotations: “[W]alks fast and fast just as if running involuntarily and unable to slow down” (*Hua’s Zhong Zang Classic* [chap-

Author Affiliation: Department of Neurology, Maryland Parkinson’s Disease and Movement Disorders Center, University of Maryland School of Medicine, Baltimore.

ter 37], dynasty 6 [AD 220-228])⁹ and “In Vienna, I saw a man above the age of fifty who was running involuntarily, being also incapable of keeping direction so as to avoid obstacles; in addition, he suffered from ptyalism” (Sagar, 1776).¹⁰

These clinical descriptions, and many others, outline a motor disorder with clear resemblance to what Parkinson described.¹¹

After publication of the 1817 monograph, the terms *shaking palsy* and *paralysis agitans* were used to describe many and varied neurologic findings that today would not be categorized as parkinsonism.¹² By 1855, there was criticism of Parkinson terminology. “The term *paralysis agitans* is essentially bad, as *paralysis* does not necessarily exist in the condition referred to.”¹³

Charcot described the resting tremor, which does not increase in severity with activity, and detailed that tremor is not required for the diagnosis of Parkinson disease. Charcot, commenting on bradykinesia, noted: “Instead even a cursory exam demonstrates that the problem relates more to slowness and execution of movement rather than to real weakness. In spite of tremor, a patient is still able to do most things.”⁸ After describing a patient with marked rigidity and no tremor, Charcot remarked that this patient “might call to question the definition given by Parkinson in his remarkable article on *paralysis agitans*.”¹⁴

The inclusion of patients with bradykinesia and no tremor under the diagnosis of Parkinson disease was accepted by Gowers¹⁵ in his 1893 textbook *A Manual of Diseases of the Nervous System*: “a difficulty arises chiefly in cases in which the tremor is absent or quite indistinct, and the evidence of the disease consists only of the loss of power and the fixity of feature and of limb, the slowness of movement, and the forward stoop. Knowledge of the significance of these symptoms, which are as characteristic as is the tremor, will prevent error.” In the same description of Parkinson disease, Gowers noted that some patients will have extension, not flexion, of the spine.

As a sequelae of epidemic encephalitis, Wilson and Bruce¹⁶ observed that there are “innumerable cases of what is now termed the parkinsonian syndrome or parkinsonism.” Wilson and Bruce made a point of separating the “disease” from the syndrome. They described characteristic features of the confirmed case (Parkinson disease), including “trunk bent forward, arms adducted and flexed at elbows . . . slow deliberate movement . . . and muscular weakness.”¹⁶ They commented on muscular weakness: “At one time I sought to avoid the use of the term ‘paralysis’ for such enfeeblement hoping it might be confined to disease of the pyramidal system; but this hope has to be modified, and so far as weakness, slowness and restriction of movement are concerned I see little material distinction between hemiplegia and *paralysis agitans*.”¹⁶

Despite the need to distinguish the disease from the syndrome, Duvoisin¹⁷ wrote, “in pre-epidemic days juvenile *paralysis agitans* was an absolute rarity, but now it is common place.” Use of the specific term *paralysis agitans* to describe juvenile cases seems to imply that the syndrome and the disease were one and the same.

In 1947, Brain¹⁸ continued this theme: “It is necessary to distinguish the parkinsonian syndrome from the conditions which may simulate it.” He described Par-

kinson disease as a disturbance of motor function characterized by slowing and enfeeblement of emotional and voluntary movements, muscular rigidity, and tremor.¹⁸ Monrad-Krohn¹⁹ described the characteristics of *paralysis agitans* in 1955, including rotary neck rigidity, stiff masklike expression, stooping with head and trunk bent forward, and small steps. No tremor was described.

Greenfield,²⁰ in his presidential address to the Second International Congress of Neuropathology in 1955, wrote, “Parkinson clearly accepted *paralysis agitans* as a disease, and this conception was accepted by Gowers and most other writers during the 19th Century. However, during more recent years, many have considered the symptoms of tremor and rigidity as a syndrome which may be caused by various lesions.” These diverse clinical descriptions and definitions beginning before 1817 through the middle 1950s describe a wide range of clinical findings defining the disease and the syndrome.

In 1962, Denny-Brown²¹ outlined the difficulty distinguishing true *paralysis agitans* from parkinsonism: “In our monograph in 1945, we made a sharp distinction between true *paralysis agitans* and arteriosclerotic parkinsonism, the former with tremor, the latter characterized by rigidity and slowness of movement. With greater experience, we have to admit that this distinction is not absolute. There is every degree of transition.”

In 1964, Monrad-Krohn and Refsum²² added to the nosologic confusion when they wrote, “Many normal associated movements disappear in extrapyramidal disturbances of the *paralysis agitans* type.” What did these well-known neurologists mean by the term *paralysis agitans* type? Or was this just a reflection of the difficulty distinguishing the syndrome from the disease? Calne,²³ in 1989, expressed the same frustration when he wrote, “It is remarkably difficult to find a clear statement of what constitutes Parkinson’s disease.”

The difficulty of an accurate clinical diagnosis of Parkinson disease was highlighted by Hughes et al.²⁴ Their study reported the pathologic findings in 100 consecutive patients clinically diagnosed as having Parkinson disease (the mean age at symptom onset was 64.5 years, and the mean disease duration at autopsy was 11.9 years). Of 100 patients diagnosed as having Parkinson disease, 76 had pathologic confirmation. The “misdiagnosed” cases included progressive supranuclear palsy, multiple system atrophy, Alzheimer disease, vascular nigral atrophy, postencephalitis, and healthy brain. This study illustrates the problems in clinical diagnosis. Of the patients misdiagnosed as having Parkinson disease, 67% had a marked initial response to levodopa treatment (>50% improvement). So much for levodopa responsiveness as a clinical criterion for the diagnosis of “true” Parkinson disease. Hughes et al,²⁴ commenting on whether Parkinson disease is a clinically diagnosable specific entity, wrote, “Until biological markers or other techniques are developed, we must accept that diverse neuropathologic disorders may produce clinical syndromes indistinguishable from Lewy Body Parkinson’s disease.”

Since Charcot, there have been numerous attempts to subdivide and make sense of the wide variability in clinical signs and symptoms in Parkinson disease. Schemes dividing Parkinson disease into bradykinesia vs tremor

early vs later onset and good or poor response to levodopa treatment have all been proposed. It is no wonder that Fahn²⁵ wrote in 1989, "Parkinson's disease, although of unknown etiology today, undoubtedly will be subdivided in the future into different varieties and etiologies."

PATHOLOGIC FINDINGS

Some authors have argued that the gold standard of diagnosis is pathologic findings, but a pathologic diagnosis may not clarify phenotypic variabilities in a syndrome. Greenfield²⁰ and Hughes et al²⁴ discussed the diversity of neuropathologic findings that may look like Parkinson disease. Since Tretiakoff's 1919 thesis,²⁶ in which he named eosinophilic inclusion bodies (corps de Lewy) and reported on the pathologic findings in 9 "typical" cases of Parkinson disease, there has not been uniformity of opinion regarding the pathologic diagnosis. Tretiakoff reported that all of his patients with Parkinson disease exhibited depigmentation of the substantia nigra and cellular degeneration, but only 6 of 9 had Lewy bodies. Since then, there have been many autopsy series of Parkinson disease in which Lewy bodies have not been 100% present.^{27,28} Rajput et al,²⁸ drawing on a unique clinicopathologic experience, makes the point that idiopathic Parkinson disease cannot be differentiated from pathologic look-alikes. There has been a certain amount of dogma in the literature that if it is Parkinson disease, there must be Lewy bodies. Although Lewy bodies are often considered hallmarks of the diagnosis of Parkinson disease,²⁹⁻³¹ Forno²⁹ writes that "[v]ery few abnormalities are pathognomonic for one disease process, and the Lewy body is not one of them." Autopsy series have an inherent bias if you define Parkinson disease as only those cases with Lewy bodies in the substantia nigra; then, of course, you can achieve 100% diagnostic accuracy of your definition. These same discussions concerning whether ubiquitinated α -synuclein inclusions need to be present to diagnose Parkinson disease continue. This debate is not settled because some of the newly discovered genetic etiologies for Parkinson disease may or may not have Lewy bodies.

GENETICS AND NOSOLOGY

The final straw that will break the nosologic back of Parkinson disease is the accumulating genetic evidence. In the past decade, there has been an enormous explosion in the discovery of genes that cause parkinsonism. At present, 5 genes have been linked to parkinsonism: α -synuclein, parkin, *LRRK2*, *DJ1*, and *PINK1*. Initially, the discovery of the α -synuclein gene in the Contursi kindred was remarkable,³²⁻³⁴ but it could be argued that there were "atypical" features in these patients, including early onset, rapid decline, and early dementia, casting doubt on whether they had Parkinson disease. Subsequently, other genes linked to parkinsonism, including *LRRK2*, *DJ1*, *PINK1*, and parkin, with the same phenotype as what is called Parkinson disease have been discovered. The pathologic features in some but not all patients with these mutations include Lewy bodies, just as in Parkinson disease.³⁵⁻³⁸

Consider the clinical diagnosis in this patient. A 39-year-old man presents with levodopa-responsive gait impairment. Six years later, freezing of gait develops, and a dopamine agonist is introduced. Nine years later, he exhibits typical parkinsonism with asymmetrical findings, continued good response to treatment, and no atypical features on examination. Most physicians would agree that this is Parkinson disease, and yet it is *PINK1* parkinsonism or *PINK1* Parkinson disease.³⁹ This is one of many examples that underscores that "patients with Parkin, PINK-1 and DJ-1 may be clinically indistinguishable not only from one another but also from age-matched patients not carrying the mutation in any of the three genes."⁴⁰ These findings demonstrate that what is often called Parkinson disease is a syndrome. It may have separate and distinct genetic etiologies. As more genes are "discovered," more causes of "idiopathic" Parkinson disease will have a distinct etiology.

Indeed, what should we call this syndrome? Published articles have variably named it *parkinsonism*; *classic, typical, or idiopathic Parkinson disease*; *Parkinson disease*; *Parkin complex*; and *Parkin Lewy body disease*. Having no desire to "defrock" James Parkinson and a fondness for eponyms, I suggest that we use the term *Parkinson diseases*. This term would remind the physician that multiple etiologies are possible to explain the patient's neurologic syndrome. It would also be useful to patients to help them understand that they are confronting a syndrome and not a disease, and it would be easier to explain the varied prognostic possibilities. Of course, the more logical approach would be to use only the descriptive term *parkinsonism* and to assign numbers to each distinct parkinsonism.

IMPLICATIONS FOR NEUROPROTECTIVE TRIALS

At the end of this discussion of the nosologic classification of Parkinson disease, the reader might simply say parkinsonism or Parkinson disease, does it really matter? The answer is yes, and it may have implications for future research regarding Parkinson disease. Is it possible that recent neuroprotective trials for Parkinson disease have failed because numerous subtypes of Parkinson disease are lumped together? We know little about how these abnormal genes, their end products, or their mechanisms of action regarding cell degeneration and cell death operate. However, each of the abnormal genes identified thus far is speculatively linked to different biological mechanisms (eg, *LRRK2* kinase activity and the parkin-ubiquitin-proteasome system), although in the end, there may be a common pathway to cell death.

The literature accepts the concept of Parkinson disease caused by specific genes, but, at the same time, parkinsonism secondary to an environmental cause (eg, carbon monoxide, manganese, or *N*-methyl-4-phenyl-1,2,3,6-tetrahydropyridine) would never be referred to as *manganese-induced Parkinson disease*. Why there is this different nosologic classification of genetic vs environmental causes of parkinsonism remains a curiosity.

Perhaps if patients with parkinsonism were stratified into etiologic groups for a disease-modifying trial, there

might be more of a chance for success. For example, if an antioxidant was the study drug, perhaps it might work with parkinsonism related to *PINK1*, or if the study drug was an enhancer of the ubiquitin-proteasome system it might work in parkinsonism related to parkin. Neuroprotection trials might be more successful if they were linked to the biological mechanism that is most likely to be responsible for the parkinsonism being studied.

As new genetic information related to parkinsonism is discovered, we will enter an era when a clinical diagnosis of parkinsonism is made and a genetic profile is ordered (parkinsonism type 1 through 30). A limited version of this has already been introduced (by Athena Diagnostics, Inc, Worcester, Massachusetts). This would be similar to the clinical and genetic diagnosis of spinocerebellar degenerations. Hopefully, each parkinsonism will eventually have a specific disease-modifying therapy. This might also represent another solution to the nosologic issue because we could drop the eponym and simply diagnose parkinsonism by the number, as we do spinocerebellar degenerations.

In conclusion, there is no single Parkinson disease. This is not so startling because L'Hermitte and Cornil,⁴¹ in 1921, proposed the same conclusion: "We must either admit that there exists in addition to multiple Parkinsonian syndromes, an authentic Parkinson's disease with particular lesions and a characteristic evolution and symptomatology or we must say that there is no Parkinson's disease just as there is no hemiplegic disease or pseudobulbar disease."

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Correspondence: William J. Weiner, MD, Department of Neurology, Maryland Parkinson's Disease and Movement Disorders Center, University of Maryland School of Medicine, 22 S Greene St, N4W46, Baltimore, MD 21201 (wweiner@som.umaryland.edu).

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