There Is No Parkinson Disease

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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.

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Battéls 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 described 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-
ter 37], dynasty 6 [AD 220-228])9 and "In Vienna, I saw a man above the age of fifty who was running involuntari-
tarily, 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 Parkin-
son described.11

After publication of the 1817 monograph, the terms
shaking palsy and paralysis agitans were used to de-
scribe many and varied neurologic findings that today
would not be categorized as parkinsonism.12 By 1835,
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. Char-
cot, 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."14 After describing a patient with marked ri-
gidity 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 ac-
cepted by Gowers15 in his 1893 textbook A Manual of Dis-
eases 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 slow-
ness of movement, and the forward stoop. Knowledge of
the significance of these symptoms, which are as char-
acteristic 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 parkinson-
ism.” Wilson and Bruce made a point of separating the “dis-
ease” from the syndrome. They described characteristic
features of the confirmed case (Parkinson disease), in-
cluding “trunk bent forward, arms adducted and flexed
at elbows . . . slow deliberate movement . . . and muscu-
lar weakness."16 They commented on muscular weak-
ness: “At one time I sought to avoid the use of the term
‘paralysis’ for such enfeeblement hoping it might be con-
fined to disease of the pyramidal system; but this hope has
to be modified, and so far as weakness, slowness and re-
striction 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 ju-
venile 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 neces-
sary to distinguish the parkinsonian syndrome from the
conditions which may simulate it.” He described Par-
kinson disease as a disturbance of motor function char-
acterized 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 Sec-
ond 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 clini-
cal descriptions and definitions beginning before 1817
through the middle 1950s describe a wide range of clini-
cal findings defining the disease and the syndrome.

In 1962, Denny-Brown21 outlined the difficulty distin-
guishing true paralysis agitans from parkinsonism: “In
our monograph in 1945, we made a sharp distinction be-
tween true paralysis agitans and arteriosclerotic parkin-
sonism, the former with tremor, the latter characterized
by rigidity and slowness of movement. With greater ex-
perience, we have to admit that this distinction is not ab-
solute. There is every degree of transition.”

In 1964, Monrad-Krohn and Refsum22 added to the
nosologic confusion when they wrote, “Many normal as-
associated movements disappear in extrapyramidal dis-
urbances 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 distin-
guishing 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 Par-
kinson disease was highlighted by Hughes et al.24 Their
study reported the pathologic findings in 100 consecu-
tive patients clinically diagnosed as having Parkinson dis-
ease (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 sys-
tem atrophy, Alzheimer disease, vascular nigral atro-
phy, postencephalitis, and healthy brain. This study il-
ustrates the problems in clinical diagnosis. Of the patients
misdiagnosed as having Parkinson disease, 67% had a
marked initial response to levodopa treatment (>50% im-
provement). So much for levodopa responsiveness as a
clinical criterion for the diagnosis of “true” Parkinson dis-
ease. Hughes et al.,24 commenting on whether Parkinson
disease is a clinically diagnosable specific entity, wrote,
“Until biological markers or other techniques are devel-
oped, we must accept that diverse neuropathologic dis-
orders may produce clinical syndromes indistinguish-
able from Lewy Body Parkinson’s disease.”

Since Charcot, there have been numerous attempts to
subdivide and make sense of the wide variability in clin-
cal 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 Fahn23 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 clinical and pathologic 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,59-61 Forno56 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 ubiquinated 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,22-24 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 Parkinson disease have Lewy bodies. Although Lewy bodies are pathognomonic for one disease process, 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 spino-cerebellar 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 spino-cerebellar 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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REFERENCES