

## PARKINSON'S DISEASE: KNOWING IT TO RECOGNIZE IT

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*[Malattia di Parkinson: conoscerlo per riconoscerlo]*

### ABSTRACT

Parkinson's disease is an idiopathic, relentlessly progressive, neurological disorder whose clinical manifestations include tremor, bradykinesia, rigidity, and postural instability. Because of the existence of multiple clinical conditions with parkinsonism and because of the lack of diagnostic hallmarks of Parkinson's disease, it is crucial to know all the clinical nuances to be able to diagnose it correctly: this brief review is intended as an aid for this purpose.

**Key words:** Parkinson's disease, parkinsonism, vascular parkinsonism, secondary parkinsonism, progressive supranuclear palsy.

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### Introduction

Parkinson's disease is one of the diseases for which clinical manifestations remain almost the only diagnostic basis available. In order to make a diagnosis, a physician can expect only a modest contribution from the most recent scientific and technological developments. From this point of view, the status of this progressively debilitating disease has not changed very much since 1817, when its clinical features were first described by the London physician James Parkinson.

When Parkinson wrote his classic monograph<sup>(1)</sup> titled "An Essay on the Shaking Palsy", he did not intend to convey a new medical discovery, but define degenerative neurological disease, known for centuries, that had never been identified as a distinct clinic entity.

The existence of tremors, associated with paralysis, had been known since Galen's times, and the term "paralysis agitans" was generally used in a vague way by the authors of medical writings. Parkinson advised against the improper use of a symptom to indicate a disease: He wrote, "Tremor

has been adopted, as a genus, by almost every nosologist; but always unmarked, in their several definitions, by such characters as would embrace this disease... Tremor can indeed only be considered as a symptom, although several species of it must be admitted".

Parkinson felt the frustration produced by the lack of certain pathophysiological acquisitions. Eager to get to the origin and the true nature of the disease regardless of the symptoms, he could only speculate, confessing in the preface, "mere conjecture takes the place of experiment; and, that analogy is the substitute for anatomical examination, the only sure foundation for pathological knowledge".

Despite these limitations, Parkinson felt a duty to publish his observations, with commendable modesty and openness to scientific debate, promising a priori "that the writer will repine at no censure" for the hasty publication of his essay provided that it would have led the anatomical pathologists of his time, more than qualified than himself by "having excited the attention of those, who may point out the most appropriate means of relieving a tedious and most distressing disease".

Parkinson's disease is one of the main causes of neurological disability in individuals over 50 years of age, with a prevalence estimated by different epidemiological surveys at 100 to 200 cases out of every 100,000<sup>(2)</sup>.

It remains a degenerative neurological disorder of unknown cause, with an insidious onset, gradually progressive course, and symptomatic drug treatment<sup>(3)</sup>.

The diagnostic criteria at onset include<sup>(4-5)</sup>:

1. Presence of the 4 cardinal motor signs: tremor, rigidity, akinesia, and asymmetrical onset
2. Check of responsiveness to drug therapy (levodopa)
3. Absence of "atypical" symptoms that warrant their exclusion, as described below.

The symptoms, at onset, in percentage are:

• tremor	50.6
• bradykinesia, rigidity, micrographia	36.6
• joint pain	20.3
• depression	10.9
• reduced balance	1.6
• dystonias	0.7
• walking with small steps	0.6
• flexed posture	0.2

The main biochemical abnormalities are:

- Marked reduction in striatal dopamine
- At death loss of dopamine > 90%

The epidemiology indicates a prevalence of around 80-200/100,000, with an incidence of 20/100,000 that increases progressively with the aging of the population up to 330/100,000 over 65 years of age<sup>(2)</sup>.

The age of onset is around 40-65 years, in some cases even much earlier or later (20-78 years); survival for Parkinson's disease is much higher than that for secondary parkinsonism and the causes of death are mainly lung or bladder infections, pulmonary embolism, and complications of falls and fractures.

The etiology of the disease remains unknown in most cases. In a small percentage of them, a genetic component has been documented (there are about 15 varieties), including mutations of the  $\alpha$ -synuclein gene (chromosome 4q) with autosomal

dominant transmission and mutations in the parkin gene (chromosome 6) in an autosomal-recessive responsible form, which accounts for about 20 to 30% of cases with onset below 40 years of age (the higher the likelihood, the earlier the onset)<sup>(6)</sup>.

The differential diagnosis is to be made with more or less different clinical pictures:

- Essential tremor
- Secondary parkinsonism
- Multiple System Atrophy
- Progressive Supranuclear Palsy<sup>(7)</sup>
- Corticobasal Degeneration
- Lewy body dementia
- Dementias
- Genetic disorders

Differential diagnosis is made primarily on clinical grounds, but the following is certainly useful:

*neuroimaging*

- Essential tremor: DaTSCAN SPECT
- Secondary parkinsonism: iatrogenic, vascular DaTSCAN SPECT, brain MRI or demyelinating<sup>(9)</sup>.
- Multiple System Atrophy, Progressive Supranuclear Palsy, Corticobasal Degeneration: IBZM SPECT, brain MRI with morphological evaluation and overall and partial brain volume definition
- Lewy body dementia: Flow SPECT, brain MRI.

Brain MRI allows you to detect the presence of gliosis of the putamen (hyperintense foci in T2 and proton density) in multisystem atrophy with possible cerebellar atrophy in OPCA, midbrain atrophy in progressive supranuclear palsy (hummingbird sign); multiple cerebral infarctions in the periventricular white matter and basal ganglia in multi-infarct parkinsonism.

The Functional Neuroimaging allows us with DaTSCAN SPECT to mark the dopaminergic terminals in the striatum and with IBZM SPECT to mark dopaminergic receptors in striatal GABAergic neurons, while the flow SPECT does not give any specific useful information.

While remaining in the context of the diagnosis of Parkinson's Disease, it is then possible to differentiate clinical subtypes so that we tend to consider the disease as a large container of polymorphic entities with clinical and pathological differences. It has been observed that the varieties of the disease characterized by the prevalence of tremor present less pronounced bradykinesia and rigidity and tend to develop less and be less debilitating than those with a prevalence of postural instability and balance disorders, typical of forms with onset

in old age: in the absence of specific clinical markers, a clear differentiation between the various conditions is possible only with anatomical and pathological findings.

## Diagnosis

Although the information and knowledge we have today the diagnosis of Parkinson's disease is not simple and reliable, as shown by anatomical and clinical correlation research studies, which have documented a possibility of diagnostic error of 25%, even after careful specialist evaluation<sup>(10)</sup>.

Therefore, in order to minimize the risk of error, especially in the early stages of the disease, when diagnostic clinical elements are still lacking, as many diagnostic discriminating elements as possible should be taken into account.

A list of key symptoms of the disease has been provided above. It is also possible to attribute so-called secondary symptoms to it. These may also occur in various early stages of the disease and include asymmetrical onset, hypomimia, sialorrhea, hypophonia, flexed posture, slow speech, depression, joint pain (ipsilateral shoulder at the onset of the disease and in particular the lumbar region), reduced blinking, micrographia.

In order to avoid the exclusion criteria, the signs and symptoms that in the early stage are incompatible with the diagnosis of Parkinson's disease are:

- Early cognitive impairment; this symptom can also be included in the diagnosis, but only after 10 years from the onset of the disease; in this case, it is much more likely that you are dealing with Lewy body dementia<sup>(11)</sup> or a form of Alzheimer's disease with an extrapyramidal component

- Early sphincter disorders: if even these may appear in the course of the disease, it seldom happens before 8-10 years of illness: the alternative diagnosis could be multiple system atrophy (MSA)

- Early instability with frequent falls: it is not part of the disease except in the late stages: an alternative diagnosis is Progressive Supranuclear Palsy (PSP)

- Osteotendinous hyperreactivity: it is a sign of pyramidal damage and hence the most likely diagnosis is multi-infarct dementia<sup>(12)</sup> or MSA

- Prevalence of symptoms only in both lower limbs: it is a typical condition of vascular parkinsonism, associated with very short steps and sphincter disorders<sup>(9)</sup>

- Presence of dystonias: these are observed only in particular cases of the disease (e.g., dopa-responsive dystonia), otherwise iatrogenic forms should be considered

- Presence of ocular motility disorders, especially vertically (typical of PSP)<sup>(13-15)</sup>;

- Presence of early and marked anterocollis: it too points to several alternative diagnosis

- Presence of blepharospasm: it is quite unusual

- Early presence of bulbar disorders (dysphagia, dysphonia, dysarthria)

- Action or reflex myoclonic events

- Cerebellar signs

- Rapid crippling course: the disease is incompatible with the need to use of orthotic devices or supports during the first 5 years of illness

- Body schema disorders

- Symmetric onset of symptoms

- Presence of sensory signs

- Intermittent or stepwise course

- Severe and incapacitating orthostatic hypotension

- Presence of the alien hand syndrome

- Syncopal episodes

- Qualitative alterations of perception and abstraction

- Eyelid apraxia

- Presence of pathological spontaneous activity assessed by electromyography

- Presence of suffering of the second motor neuron

- Insensitivity to treatment with l-dopa at the appropriate dose.

Despite the limitations of mainly clinical criteria, those listed above certainly provide adequate guidance to navigate reliably through the diagnosis of Parkinson's disease, with the awareness that even if scrupulously applied, there still is a certain margin of error, as diagnostic certainty can only be achieved at an anatomo-pathological level.

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