

# DIAGNOSTIC PITFALLS IN PARKINSON'S DISEASE

## Case report

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**ABSTRACT** - Parkinson's disease (PD) is characterized by resting tremor, rigidity and bradykinesia. In 80% of cases, the disorder begins with upper limb resting tremor. However, there are some presenting atypical features that make the diagnosis even more difficult and intriguing. The disorder can have its onset below 40 years old, characterizing early-onset parkinsonism, which differential diagnosis possibilities are varied. Atypical presentations include a pure akinetic-rigid syndrome, the initial manifestations occurring in the lower limbs, and pain as the most important or sole manifestation. These atypical features are unusual, but can be seen in clinical practice. We present a 37 years old woman with early-onset parkinsonism beginning with an akinetic-rigid syndrome in the lower limbs whose first symptom was left leg pain, which diagnosis was made after 4 years of onset and after 16 referrals to several experts in different fields. We discuss these atypical features and the diagnostic pitfalls in PD.

**KEY WORDS:** Parkinson's disease, parkinsonism, pain.

### Dificuldades diagnósticas na doença de Parkinson: relato de caso

**RESUMO** - A doença de Parkinson (DP) caracteriza-se pela tríade de tremor, rigidez e bradicinesia. Em cerca de 80% dos casos inicia-se com tremor em membros superiores. Entretanto, certas atipias na apresentação desta entidade tornam seu diagnóstico ainda mais desafiador. A doença pode iniciar-se abaixo dos 40 anos de idade, caracterizando o parkinsonismo de início precoce. Apresentações atípicas incluem uma síndrome rígido-acinética pura, as manifestações inaugurais ocorrendo em membros inferiores, e uma síndrome dolorosa podendo ser um sintoma inicial proeminente ou o único sintoma. Estas atipias, apesar de infreqüentes, são encontradas na prática clínica diária. Discutimos estas características atípicas ao apresentarmos uma paciente de 37 anos com quadro rígido-acinético de instalação precoce, iniciado em membros inferiores, cujo sintoma predominante era dor, cujo diagnóstico somente foi feito após 4 anos do início e após 16 avaliações médicas por vários especialistas. Discutiremos as dificuldades diagnósticas que os médicos podem encontrar quando da avaliação de pacientes com DP.

**PALAVRAS-CHAVE:** doença de Parkinson, parkinsonismo, dor.

Parkinson's disease (PD) is a chronic disorder, characterized by rest tremor, rigidity and bradykinesia, due to loss of neurons in some cerebral regions, especially in substantia nigra (SN) *pars compacta*<sup>1</sup>. It usually affects individuals over 50 years of age, symptoms starting more commonly in upper limbs. Tremor is generally the initial manifestation, and clinical asymmetry of symptoms is the rule. However, some atypical features may be present, what makes the diagnosis even more difficult or delayed, such as disease starting in individuals under 40 years old, lower limbs being affected first, and pain being the first

symptom of the disease. These features demand a broader differential diagnosis. We report a 41-year-old woman with PD, whose first symptom was pain in lower limbs, which led her to several specialists until the definitive diagnosis. We aim to expose the existence of atypical forms of PD, so contributing to improve the degree of suspicion for the uncommon variants of this affection.

### CASE

In July 1996, a previously healthy 37-year-old female patient presented pain in her left leg, located on the groin, radiating up to lumbar region and down to the thigh. The

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pain was constant, but would get much worse when she walked, halting her from ambulating normally. From July 1996 to December 1996, she sought four orthopedists, performed lumbar spine X-ray and bone scintigraphy, and received two diagnoses, lumbar pain and coxofemoral joint affection, and anti-inflammatory were prescribed, with no relief of the symptoms. A lumbar root anesthetic block with lidocaine was tried, without improvement. For the coxofemoral joint disease, a surgical intervention with placement of coxofemoral prosthesis was advised, which was promptly refused by the patient. Besides the pain, in October 1996, she had started to feel numbness in the left leg. The patient continued to complain of walking difficulties, ultimately needing a cane to ambulate. In December 1996, due to lack of therapeutic response, she was advised by the last orthopedist to seek for acupuncture and psychiatric treatment. Acupuncture was not of any help, as well as the use of anxiolytics.

In June 1998, the patient looked for the fifth orthopedist who ordered a four-member electromyogram that was normal. The orthopedist ruled out organic disorders, and advised her to seek for a second psychiatrist, which the patient refused, returning to the prior orthopedist. The pain started to abate slowly, allowing the patient to walk without the aid of the cane, but the "numb leg" feeling was getting worse, leading her to drag the left lower limb. In November 1998, she sought for the sixth orthopedist who suspected of an inguinal hernia, referring her to a gastroenterologist. An abdomen ultrasound exam was ordered, which ruled out this diagnosis. She was advised to seek for an orthopedist or a neurologist. At that time, she was starting to complain of an ill-defined sensation in the left arm. She looked for the seventh orthopedist, which referred her to a neurologist.

The patient underwent the first neurological evaluation in February 1999. An electroencephalogram (EEG) and a head computed tomography (CT) were ordered, which were normal, and with these results the neurologist ruled out any neurological abnormalities. Two months later she consulted the second neurologist who ordered a new head CT and EEG, which were normal. A cerebral arteriography was indicated to investigate for stroke, which was refused by the patient. In the months that followed, the motor problems continued to get worse, interfering even more with gait and activities of daily living (ADL). There was almost no pain. In October 1999, she consulted a neurosurgeon who examined her, revised all the procedures performed, but did not get to a definitive diagnosis.

From December 1999 to April 2000, a general practitioner and a physician expert in psychosomatic disorders evaluated her. The latter ordered a new bone scintigraphy, which was normal, and referred her to a second neurosurgeon, who diagnosed fibromyalgia. In September 2000, as the patient would not improve with the current treatment, she sought for the third neurologist, who ordered a magnetic resonance of the brain which was normal. In October 2000 the patient was evaluated by the eighth orthopedist, who ordered a coxofemoral joint ultrasound, which was also normal, and an orthopedic illness was definitely ruled out.

In November 2000, the patient was seen at the Movement Disorders Outpatient Clinic Division of Neurology of the Hospital das Clínicas de São Paulo. Besides the previous data, there was no noteworthy medical or family history. A rigid-akinetic syndrome affecting the left hemibody was noticed, leading to writing and gait difficulties, with a tendency to the patient walk on her toes on the left side. There were no other neurological or cognitive abnormalities. Based on the clinical picture, lack of abnormalities on neuroimaging and copper metabolism tests, a diagnosis of early-onset Parkinson's disease was made. The patient underwent a treatment challenge with levodopa/benserazide 200 mg/50 mg in an initial dose of 1/2 tablet three times daily. As there was no improvement after the first week of treatment, the dose was titrated up to 1 tablet three times daily. After ten days, a clear improvement in motor performance was observed, as reflected by gait, ADL and professional activities, especially with improvement in her typing skills. Afterwards, as a treatment maintenance strategy, a reduction in levodopa total dose was possible with association of the dopaminergic agonist pramipexol. This therapeutic regimen was kept with good control of motor difficulties. Posteriorly, amantadine was added to the treatment scheme to better control the parkinsonian symptoms.

In the following months, the parkinsonian syndrome started to affect the right hemibody. After three years of treatment, the patient started to experience dose-peak dyskinesias, more on the left side. Dyskinesias progressively increased in severity, demanding reduction of the dose of dopaminergic agents, leading to subsequent worsening of parkinsonian symptoms. This problem was overcome by performance of right postero-ventral pallidotomy, to obtain a better control of dyskinesias and of the parkinsonism, even with lower doses of dopaminergic drugs.

The Ethics Committee of our institution approved this article and the patient gave full informed consent.

## DISCUSSION

The diagnosis of PD in this patient was difficult to make because of the several atypical features presented, such as age at onset below the usually seen, pain as the first clinical manifestation, absence of rest tremor, and beginning of the illness in the lower limbs. PD usually starts in middle-aged individuals, with a prevalence of about 2% after 65 years of age<sup>2</sup>, but 4 to 12% of PD cases start before 40 years of age, characterizing early-onset PD<sup>3</sup>. In these cases, differential diagnosis is rather broad, and one should consider genetic forms of the illness, such as PARK 2 (*parkin*), PARK 6 (*PINK1*), and PARK 7 (*DJ-1*). However, the detection of these mutations is not yet available in clinical practice, and its diagnosis would not alter treatment<sup>4,5</sup>.

Other diseases that may have parkinsonian features as their initial manifestations should be consid-

ered in the differential diagnosis of early-onset PD, such as dopa-responsive dystonia (DYT5), Wilson's disease (ruled out in this patient with the appropriate laboratory tests), juvenile form of Huntington's disease, type 2 and 3 spinocerebellar ataxias, rapid-onset dystonia-parkinsonism (DYT12), and neuroacanthocytosis, besides toxic and metabolic cause of parkinsonism<sup>6</sup>. In this patient, the slow disease progress, the normal imaging procedures, the good response to levodopa and the absence of any personal and family medical history allowed us to rule out all these possibilities.

Regarding to the phenomenon of pain in PD, it can at times occur in the early years of the illness. This symptom, when the disease is not yet full-blown, usually leads the patients to seek other medical specialties, in which the degree of suspicion for PD is not as high as in neurology, often leading to a delay in the diagnosis, as happened in our case. Gilbert<sup>7</sup> reports a 65-year-old patient who sought for medical advice due to a 2-year-long pain in her arms that, following extensive orthopedic evaluation, was discovered to be caused by PD after a tremor in her right leg appeared.

Pain may be related to the akinetic-rigid syndrome even when it is slight enough to be clinically recognizable. However, there are other mechanisms involved. Pain in PD was initially considered to be an analogous of post-stroke central pain syndromes<sup>8</sup> but, different from these, there is increased evoked pain sensitivity to thermal stimuli, whereas in central pain disorders there was a decrease in these responses<sup>9</sup>.

The neurodegenerative process in PD may lead to interruption of pain-inhibitor dopaminergic and nigral descendent pathways from the mesencephalon, thus liberating nociceptive activity in the first neuron of the dorsal root. This neurodegeneration process may also initiate a cascade of hypersensitivity to painful stimuli in basal ganglia and other rostral areas<sup>8,9</sup>. However, levodopa does not appear to improve spontaneous pain<sup>8</sup>. In PD, there is not only loss of dopaminergic neurons, but also other neurotransmitter systems are involved, such as serotonergic, cholinergic, noradrenergic, and peptidergic neurons<sup>1</sup>. It is likely that loss of cell in other brain regions such as *locus coeruleus*, pontine tegmental area, anterior cingulate gyrus, insula, medial thalamic nucleus, amygdala, and hypothalamus, have a role in the generation of pain in PD. These regions modulate ascendant nociceptive pathways through noradrenergic afferents<sup>8</sup>.

The form of PD that begin with an akinetic-rigid syndrome is more difficult to diagnose than when the classic resting tremor is present. This type of presentation occurs in about 20% of PD cases<sup>1</sup>, and the time lag between the initial manifestations and its diagnosis is always greater than the one observed in the tremor-dominant syndromes. The cases of PD that start with an akinetic-rigid syndrome usually evolve faster, and gait and stance disturbances occur more frequently. Occasionally, cognitive abnormalities in the form of a dysexecutive syndrome may occur in this group of individuals<sup>10</sup>. Some studies demonstrate that early-onset PD patients most often present the tremor-dominant type of disease<sup>6,11,12</sup>. Lewis et al.<sup>10</sup>, however, argue against this information.

Our patient presented her initial manifestations in her lower extremities, a quite rare atypical feature in PD. Most often, PD starts in the upper limbs<sup>13</sup>, but in about 20% of cases it can begin in the legs<sup>14</sup>.

SN is a quite heterogeneous nucleus, with regional variations in its striatal projections and in the distribution of its biochemical markers. *SN pars compacta* is divided into a ventral and dorsal tiers. The lateral and ventral regions send efferents to the dorsal putamen, whereas neurons dorsally located in the SN project to the ventral regions of the caudate nucleus. The lateral and posterior parts of the SN are related to the dorsal and lateral regions of the putamen<sup>15</sup>. There are no data concerning somatotopic organization of the *SN pars compacta*, but there is clear somatotopic correlation between motor cortical areas and the putamen<sup>16,17</sup>.

Fearnley and Lees<sup>16</sup> in a pathologic study of 50 PD cases, and Damier et al.<sup>18</sup> in a immunohistochemistry study of five cases of PD, demonstrated that the degenerative process in the *SN pars compacta* starts in its ventral tier, specially in the lateral region, extending further to the medial region. One would expect the symptoms to begin in the lower limbs. Fearnley and Lees<sup>16</sup> suggest that the small deficits in the hands are soon perceived, and that these same clinical abnormalities in the feet and legs can be missed in the early years of disease, what could explain this paradox. The authors argue that dystonia in young-onset PD usually starts in the legs, not involving the arms. Lewis et al.<sup>10</sup> argue against this theory, stating that it does not explain all the PD cases that begin in the lower limbs. This issue needs to be further elucidated.

Vidailhet et al.<sup>17</sup> in a prospective study of 20 PD patients observed the symptoms to begin in the low-

er limbs in a third of the cases, or preceding or evolving along with the symptoms in the upper limbs. The authors state that doctors pay less attention to the legs when evaluating early-onset PD patients. Besides, according to the authors and to Fearnley e Lees<sup>16</sup>, parkinsonian symptoms in the arms are easier to be detected, as far as minimal functional abnormalities may alter hands fine movements, whereas the movements of the legs and feet are simpler, and minimal deficits may go unnoticed. However, Schelosky and Poewe<sup>13</sup> in a study of 250 PD cases demonstrated that the disease predominantly affects upper limbs in the beginning.

In the cases starting in the lower limbs, the first symptoms may be rest tremor, or a hypokinetic-rigid syndrome, as in the case described here.

For all those reasons presented, one can understand why PD in this patient was diagnosed only after 4 years from the onset, during which period the patient looked for 8 orthopedists, 3 neurologists, 2 neurosurgeons, 2 psychiatrists, and one gastroenterologist, summing 16 doctors. It must be emphasized that the good response to levodopa along with the development of levodopa-induced dyskinesias was a valuable proof to make the diagnosis.

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