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**Abstract**

**Introduction:** Diagnosis of Parkinson's disease (PD) is mainly based on clinical features. Accurate neurological examination is required but dopamine transporter (DaT) single photon emission computed tomography (SPECT) could be perfomed to support the diagnosis in ambiguous cases. The aim of this work is to describe the characteristics of patients with a prolonged PD misdiagnosis.

**Methods:** We collected data from 24 patients initially diagnosed with PD who had an atypical long-term evolution. We analyzed demographic and clinical characteristics and antiparkinsonian drugs medication. Brain MRI, DaT-SPECT and/or accelerometry/electromyography (EMG) recording were performed in a subgroup of patients. We analyzed the causes of erroneous PD diagnosis as well as the final diagnoses.

**Results:** Mean age at PD diagnosis was 60.4 ± 14.8 years. Symptoms at onset were rest tremor (n=19), gait instability (n=7) and micrographia (n=4). Mean duration before diagnosis correction was 8.4 ± 5.3 years. All patients were treated by antiparkinsonian drugs with a mean daily LEVODOPA equivalent dose (LED) of 508.1± 528.4 mg. All 18 patients who underwent DaT-SPECT had a normal result. The most frequent final diagnoses were essential tremor (n=11) and functional movement disorders (n=9).

**Conclusion:** Cases that have been initially diagnosed as PD and then progress in an atypical long-duration fashion may have been misdiagnosed. Absence of genuine bradykinesia, non-sustained response to antiparkinsonian drugs, or absence of LEVODOPA-related side effects should prompt the clinician to reappraise the diagnosis and to consider performing a DaT-SPECT.

**Abbreviations**

DaT: dopamine transporter

EMG: electromyography

ET: essential tremor

FMD: functional movement disorders

LED: LEVODOPA equivalent dose

LRRK2: leucine-rich repeat kinase 2

MDS: Movement Disorder Society

PD: Parkinson's disease

SD: standard deviation

SWEDD: scans without evidence of dopaminergic deficit

**Keywords:** Parkinson's disease, essential tremor, functional movement disorders, DaT-SPECT

## Introduction

The diagnosis of Parkinson's disease (PD) is mostly based on clinical examination. It can be guided by the Movement Disorder Society (MDS) clinical diagnostic criteria [1,2], and occasionally supported by imaging studies in challenging cases. Definite diagnosis can only be achieved by *post mortem* neuropathological examination [3]. The accuracy of PD diagnosis in clinical practice is suboptimal, notably in the early stages, when manifestations of the disease have not fully emerged [4]. Initial PD diagnosis is overall reconsidered in 10-30% of the patients during the follow-up [4-7]. There is a trend towards over-diagnosis of PD [4,8] but the diagnosis accuracy seems to increase when patients are examined in a specialized Movement Disorders unit and with disease duration, as confirmed by autopsy data [9,10]. In specialized centers it is easier to access specific investigations to rule out differential diagnosis and invalidate PD diagnosis. Normal dopamine transporter (DaT) SPECT rules out PD, as reported in the MDS absolute exclusion criteria [1]. Advances in biological and radiological biomarkers research are promising, notably in the differentiation between PD and atypical parkinsonism [11]. Currently, there is no specific PD biomarker that can allow us to ascertain the diagnosis of PD in patients with a neurodegenerative disorder so that clinical diagnosis remains the gold standard.

We aimed to describe the clinical features involved in erroneous PD diagnosis during a long-erm clinical follow-up and to revise diagnosis in those atypical PD patients.

## Methods

To describe the features involved in erroneous initial diagnosis of PD, we retrospectively analyzed a series of PD patients, who had had an atypical long-term evolution. Patients were followed up in two French sites, at Neurology Department of Pitié-Salpêtrière Hospital in Paris (n = 22) and Neurology Unit of Avicenne Hospital in Bobigny (n = 2), between 2010 and 2018.

The study was approved by the local ethics committee (CPP-IdF-Paris 6). According to the French law concerning clinical retrospective studies, a written consent of patients was not mandatory. An oral consent was nevertheless obtained for all patients. For video recording a written consent was obtained.

The atypical evolution of PD was defined by the presence of at least one of the following features: stability of neurological examination after several years of follow-up (the absence of disease stage worsening with no change in drug doses, no use of walking devices, etc.), absence of genuine bradykinesia (progressive decrements in velocity and/or amplitude movements), non-sustained response to dopaminergic treatments, absence of LEVODOPA-induced motor complications after 10 years of LEVODOPA therapy. PD diagnoses were revised by applying the PD diagnostic criteria of Postuma et al., 2015 [1]. We collected demographic, clinical, radiological and therapeutic data. Motor examination was assessed by the third section of the Unified Parkinson's Disease Rating Scale (UPDRS, max. value 108). The mean daily LEVODOPA equivalent dose (LED) was calculated for each patient. Brain MRI, Dat-SPECT and/or accelerometry/electromyography (EMG) recordings were performed in a subgroup of patients, when diagnostic uncertainty persisted after a rigorous clinical examination based on the latest PD criteria [1]. Data are expressed as the mean ± standard deviation (SD) or frequency (n).

**Results**

PD diagnosis was reassessed in 24 patients (19 women and 5 men). Demographic, clinical and radiological characteristics of all patients are summarized in Table 1. The initial PD diagnosis was performed in the half of patients by family physician and in the other half by a neurologist who did not work in a movement disorder center. Mean age at PD diagnosis was 60.4 ± 14.8 years, and mean age at examination was 68.8 ± 16.3 years with a mean disease duration of 8.4

± 5.3 years. Symptoms at onset (isolated or combined), were rest tremor (n = 19), gait instability (n = 7), akineto-rigid syndrome (n=4), and/or micrographia (n = 4). UPDRS was available from referral letters in only 7 patients at the time of reassessment, with a mean score of 12.9 ± 7.7, ranging from 3 to 25 (max value 108). During neurological reevaluation, we assessed UPDRS only in 4 patients with a mean score of 10.5 ± 5.2; for the other patients, the scale was not performed since parkinsonian syndrome was absent or not obvious. All patients were receiving oral antiparkinsonian drugs with a mean daily LED of 508.1 ± 528.4 mg. Amongst them, eight patients were receiving high dose of LED (≥ 600 mg), without any clinical improvement. The main clinical features which led us to question the diagnosis were: paucity of bradykinetic features (n=13), non-sustained response to antiparkinsonian drugs (n=6), absence of side effects (dyskinesia, motor fluctuations, wearing off) of antiparkinsonian drugs despite long disease duration (n=6), and evidence for distractibility and/or suggestibility during clinical examination (n=8).

DaT-SPECT was performed and normal in 18 patients. Twelve patients underwent a brain MRI, showing vascular leukoencephalopathy signs (n = 5), bilateral pallidal lesions (n = 1), imaging findings of normal pressure hydrocephalus (n = 1) and cerebral falx meningioma (n = 1). MRI was normal in four patients. EMG and accelerometry were performed in two patients and showed findings inconsistent with a parkinsonian tremor, but rather a typical pattern of essential tremor (ET) recording in one patient, and fluctuations of the tremor frequency and intensity, influenced by distraction, in another. Based on clinical reevaluation and additional examinations, we revised the initial PD diagnosis. Final diagnoses were ET (n= 11), functional movement disorders (FMD) (n= 9), and individual cases of normal pressure hydrocephalus, anoxic brain injury as revealed by bilateral pallidal lesions on brain MRI, previous neuroleptic drug treatment, and association of lumbar spinal stenosis and cerebral falx meningioma. An autosomal dominant transmission pattern was observed amongst the 5/11 ET cases. Withdrawal

of dopaminergic drugs did not result in worsening of the symptoms in any patient (24/24). Video 1 shows one patient with FMD diagnosis after evolution over 15-year period and no improvement with LEVODOPA treatment. The absence of characteristic bradykinesia, without decrease in hand movements speed and amplitude, can be observed in the video.

**Discussion**

We report data from 24 patients with prolonged PD misdiagnosis, who underwent a late clinical reassessment in a specialized Movement Disorders clinic. This case series underlines the importance of reassessing PD patients when the course of the disease is unexpected.

In our cohort, ET and FMD were the most frequent diagnoses. ET has previously been reported as the main differential diagnosis in other series of presumed PD patients [5]. One reason is that ET is one of the most frequent movement disorder with an overall prevalence of 0.9%, which increases with age [12]. Neurologists should be cognizant of the key clinical features which assist in establishing the correct ET diagnosis [13]. Likewise, functional neurological disorders are frequent in clinical practice, accounting for 4-16% of newly referred neurological patients [14], or even more in specialized Movement Disorders clinics. These disorders are frequently unrecognized for a long period possibly due to limited clinical experience of neurologists and psychiatrists with this disorder. This diagnosis delay often results in stress and disability, thereby representing a considerable economic burden [15]. Of note, tremor and dystonia are the main clinical presentation among FMD [15, 16]. When examining patients with tremor, clinicians should look for positive signs of FMDs notably distractibility, entrainment suggestibility and variability [17]. EMG and accelerometry can support the clinical diagnosis of functional tremor or dystonia [18] and may be helpful in explaining the diagnosis as the starting point of the therapeutic strategy.

To avoid misdiagnosis in PD, clinicians should know how to recognize the classical features of parkinsonian syndrome. For example, progressive reduction in speed and amplitude of repetitive movements is characteristic of parkinsonian brady- and hypokinesia, respectively, while it is not present in patients with movement limitations caused by osteoarticular pathologies, spastic hypertonia, or functional slowness. Moreover, in functional parkinsonism, tremor usually involves the limb rather than the hand, with fluctuations in rhythm and direction, rigidity is due to an active resistance and not associated with cogwheel, freezing of gait is absent, handwriting is impaired without the typical micrographia [19]. In addition, disability is faster attained and is not proportionate to what could have been expected from clinical examination. Interestingly, functional movement disorders can coexist with PD and are more frequent in PD and dementia with Lewy bodies than in other neurodegenerative disorders and psychiatric diseases [20]. Finally, we suggest that the diagnosis of PD should be reappraised when LEVODOPA treatment is ineffective and when there is no motor LEVODOPA-induced complications. These complications occur in about 50% of PD patients after 5 years [21] and in 90% of patients after 10 years of evolution. We did not detect any atypical parkinsonian cases. It may be explained by the low prevalence of these diseases compared to ET and FMD, and by the limited number of subjects included in our study. Moreover, in atypical parkinsonian syndromes, additional symptoms and signs (red flags), as well as the rapid course of the disease, usually induce a faster correction of the misdiagnosis.

Imaging studies may be required to correct a wrong diagnosis of PD. Indeed, brain MRI may guide towards differential diagnoses such as atypical parkinsonian syndromes, as may [18F]-Fluorodeoxyglucose ([18F]-FDG) PET and sympathetic cardiac [123I]-Metaiodobenzylguanidine ([123I]-MIBG) scintigraphy [6, 22]. DaT-SPECT can be helpful in doubtful cases [7,8]. Normal DaT-SPECT usually eliminates PD diagnosis, and conversely, when abnormal, it supports physician confidence in PD diagnosis with consistent modifications

in clinical management [7]. However, patients with suspected PD, whose DaT-SPECT show no evidence of dopaminergic deficit (SWEDD) still represent a controversy. It seems clear that the majority of SWEDD patients are misdiagnosed as PD [23, 24], and wrongly enrolled in clinical trials [19, 25]. Some exceptions exist as reported for SWEDD in a patient carrying leucine-rich repeat kinase 2 (LRRK2) p.G2019S mutation [26]. In a three-year longitudinal study, specificity of DaT-SPECT to detect nigrostriatal denervation was almost 100%, without modification all along the study, showing overdiagnosis of PD at the baseline [8]. However, normal DaT-SPECT has been described at the early stages of the disease [27] and conversion of normal to abnormal scans can occur during follow-up [28]. DaT-SPECT can support the clinical and electrophysiological diagnosis of functional parkinsonism hence limiting misdiagnosis [29].

Misdiagnosis has a significant impact on treatment and prognosis for patients but also influences the outcomes of epidemiological and clinical studies. Misdiagnosis rates should be taken into account to calculate sample size, especially when early-onset patients are included in clinical researches. For this purpose, the MDS task force proposed criteria for clinically established early PD [30] with modifications of the MDS criteria [1], as shown in Table 2. These criteria have a high specificity (95.4%) in early PD patients and are a useful tool to accurately recruit patients in clinical trials.

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**Video 1-2. Patient with functional movement disorders diagnosis showing absence of bradykinesia (video 1) and evidence of normal right upper limb mobility suggesting distractibility (video 2).**

| Sex | Age at PD diagnosis (y) | Clinical examination | LED (mg/d) | DD (y) | DaT-SPECT | Brain MRI | accelerometry/ EMG | Atypical features | Reason for diagnosis reevaluation | Final diagnosis |
|---|---|---|---|---|---|---|---|---|---|---|
| F | 66 | Akineto-rigid syndrome, jaw and UL rest tremor, UL postural tremor, gait impairment, orthostatic hypotension | 300 | 12 | N | N | nd | 12 years evolution without LID or motor fluctuations | normal DaT-SPECT | ET |
| F | 48 | Akinesia, rest tremor, gait impairment, swallowing disorder, urinary dysfunction, restless legs syndrome | 450 | 15 | N | nd | nd | 15 years evolution with stability of symptoms without LID | Distractibility at examination, two DaT-SPECT negative | FMD |
| F | 46 | Akineto-rigid syndrome, rest tremor, swallowing disorder, urinary dysfunction, gait impairment | 2711 | 6 | N | nd | nd | Stability of symptoms, no motor fluctuations | Distractibility during neurological evaluation, normal DaT-SPECT | FMD |
| F | 32 | Akineto-rigid syndrome, rest tremor | 625 | 6 | N | nd | nd | Stability of symptoms, no motor fluctuations | Distractibility during neurological evaluation, normal DaT-SPECT | FMD |
| F | 58 | Akineto-rigid syndrome, rest tremor, gait impairment, restless legs syndrome | 555 | 15 | N | VLE | nd | 15 years evolution without clinical worsening | Neuroleptic intake | Iatrogenic |
| F | 55 | Akineto-rigid syndrome, rest tremor | 245 | 2 | nd | nd | nd | Stability of symptoms, no motor fluctuations | Distraction and suggestibility during clinical examination | FMD |
| F | 73 | UL rest and postural tremor | 52 | 3 | N | nd | nd | Predominant tremor with no fatigable bradykinesia | normal DaT-SPECT | ET |
| F | 68 | UL rest and postural tremor, gait impairment | 257.5 | 15 | Nd | VLE | nd | Predominant tremor with no fatigable bradykinesia | 12 years evolution without treatment positive effect | ET |
| M | 55 | Gait impairment, sensory dysfunction | 100 | 5 | N | Nd | nd | Stability of symptoms, no motor fluctuations | Distraction and suggestibility during clinical examination, normal DaT-SPECT | FMD |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| F | 46 | Akineto-rigid syndrome, gait impairment | 840 | 6 | N | N | nd | Stability of symptoms, no motor fluctuations, no response to treatment | Distraction and suggestibility during clinical examination, normal DaT-SPECT | FMD |
| F | 63 | UL rest and postural tremor | 750 | 10 | N | nd | nd | Stability of symptoms, no motor fluctuations, no fatigable bradykinesia, no response to treatment | Normal DaT-SPECT | ET |
| M | 49 | Akineto-rigid syndrome, rest tremor, pyramidal syndrome, gait impairment, urinary dysfunction, sleep disorders | 105 | 7 | N | BPL | nd | Mild extrapyramidal syndrome, cerebellar and pyramidal syndrome | BPL at brain MRI | Anoxic brain injury (bilateral pallidal lesions) |
| F | 75 | Akineto-rigid syndrome, pyramidal syndrome gait impairment, urinary dysfunction, orthostatic hypotension | 850 | 9 | N | CFM | nd | Aggravation of pyramidal syndrome and gait impairment, no response to treatment | Lumbar spinal stenosis at spine MRI; cerebral falx meningioma at brain MRI | Lumbar spinal stenosis |
| F | 44 | Akineto-rigid syndrome, gait impairment, limb dystonia, urinary dysfunction, sleep disorders | 700 | 11 | N | N | nd | Long term stability of symptoms, no motor fluctuations, no response to treatment | Distraction and suggestibility during clinical examination, normal DaT-SPECT | FMD |
| F | 74 | UL rest and postural tremor, gait impairment | 600 | 10 | N | VLE | nd | 10 years evolution without LID or motor fluctuations | Normal DaT-SPECT | ET |
| F | 81 | Akinesia, UL rest and postural tremor | 500 | 3 | nd | nd | nd | predominant tremor with no fatigable bradykinesia, no response to treatment | Second clinical evaluation positive for ET and negative LEVODOPA - sensibility | ET |
| M | 75 | Gait impairment, urinary dysfunction, cognitive dysfunction | 250 | 4 | nd | NPH | nd | Gait impairment aggravation, cognitive decline, urinary dysfunction | NPH at brain MRI | NPH |
| F | 30 | UL rest and postural tremor, gait impairment, sleep disorders | 54 | 2 | N | N | nd | Predominant tremor with no fatigable bradykinesia | Normal DaT-SPECT | ET |
| M | 75 | UL rest and postural tremor | 608 | 15 | nd | nd | nd | Predominant tremor with no fatigable bradykinesia | Long term stability of symptoms, no motor fluctuations | ET |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| F | 66 | UL postural tremor | 392.5 | 20 | N | nd | nd | Predominant tremor with no fatigable bradykinesia, primidone efficacy | Normal DaT-SPECT | ET |
| F | 70 | Rest and postural tremor | 300 | 15 | N | VLE | Rest, postural and action tremor with frequency variability (4.5-6 Hz) and loss by distraction | Long term stability of symptoms, no motor fluctuations, no response to treatment | Distraction and suggestibility during clinical examination | FMD |
| M | 52 | UL postural tremor | 450 | 5 | N | Nd | UL attitude tremor with frequency of 6 Hz associated to rest tremor | Predominant tremor with no fatigable bradykinesia, 5 years evolution without LID or motor fluctuations | Normal DaT-SPECT and typical accelerometry EMG | ET |
| F | 64 | Dysphonia, head and UL rest and postural tremor | 375 | 3 | N | VLE | nd | Stability of symptoms, no motor fluctuations | Distraction and suggestibility during clinical examination | FMD |
| F | 84 | UL, jaw, head rest and postural tremor | 125 | 3 | nd | Nd | nd | Predominant tremor with no fatigable bradykinesia | Stability of symptoms, no motor fluctuations | ET |

**Table 1. Demographic, clinical and radiological characteristics of our cohort of patients.**

**Abbreviations:** BPL: bilateral pallidal lesions; CFM: cerebral falx meningioma; DD: disease duration; ET: essential tremor; F: female; FMD: functional movement disorders; LID: LEVODOPA-induced dyskinesia; M: male; N: normal; nd: not done; NPH: normal pressure hydrocephalus; UL: upper limb; VLE: vascular leukoencephalopathy.

**Table 2. Differences between the new MDS criteria for clinically established early PD and MDS clinical diagnostic criteria for PD.**

| | MDS Clinical Diagnostic Criteria for Clinically Established PD [1] | MDS Clinical Diagnostic Criteria for Clinically Probable PD [1] | MDS Criteria for Clinically Established Early PD (<5 years) [30] |
|---|---|---|---|
| **Essential criterion** | Parkinsonism (bradykinesia, in combination with at least 1 of rest tremor or rigidity) | Parkinsonism (bradykinesia, in combination with at least 1 of rest tremor or rigidity) | Parkinsonism (bradykinesia, in combination with at least 1 of rest tremor or rigidity) |
| **Supportive criteria** | At least two<br>- Clear and dramatic beneficial response to dopaminergic therapy<br>- Presence of LEVODOPA-induced dyskinesia<br>- Rest tremor of a limb<br>- Presence of either olfactory loss or cardiac sympathetic denervation on MIBG scintigraphy | If 1 red flag → at least 1 supportive criterion<br>If 2 red flags → at least 2 supportive criteria are needed<br>No more than 2 red flags | Removed |
| **Red flags** | No red flags<br>- Rapid progression of gait impairment requiring regular use of wheelchair within 5 y of onset<br>- A complete absence of progression of motor symptoms or signs over 5 or more y unless stability is related to treatment<br>- Early bulbar dysfunction within first 5 y<br>- Inspiratory respiratory dysfunction<br>- Severe autonomic failure in the first 5 y of disease<br>- Recurrent (>1/y) falls because of impaired balance within 3 y of onset<br>- Disproportionate anterocollis (dystonic) or contractures of hand or feet within the first 10 y<br>- Absence of any of the common non motor features of disease despite 5 y disease duration<br>- Otherwise-unexplained pyramidal tract signs<br>- Bilateral symmetric parkinsonism | | Red flags considered as absolute exclusions |
| **Exclusion criteria** | Absence of absolute exclusion criteria<br>- Unequivocal cerebellar abnormalities<br>- Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades<br>- Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, within the first 5 y of disease<br>- Parkinsonian features restricted to the lower limbs for more than 3 y<br>- Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism | Absence of absolute exclusion criteria<br>(9 exclusion criteria) | Absence of absolute exclusion criteria<br>- Unequivocal cerebellar abnormalities<br>- Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades<br>- Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia<br>- Parkinsonian features restricted to the lower limbs<br>- Treatment with a dopamine receptor blocker or a dopamine-depleting agent in a dose and time-course consistent with drug-induced parkinsonism<br>- Absence of observable response to high-dose LEVODOPA despite at least moderate severity of disease |

| | | | |
|---|---|---|---|
| | - Absence of observable response to high-dose LEVODOPA despite at least moderate severity of disease<br>- Unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia<br>- Normal functional neuroimaging of the presynaptic dopaminergic system<br>- Documentation of an alternative condition known to produce parkinsonism | | - Unequivocal cortical sensory loss, clear limb ideomotor apraxia, or progressive aphasia<br>- Normal functional neuroimaging of the presynaptic dopaminergic system<br>- Gait impairment requiring regular use of wheelchair<br>- Severe dysphonia/dysarthria and/or severe dysphagia<br>- Inspiratory respiratory dysfunction<br>- Severe autonomic failure<br>- Recurrent (>1/y) falls because of impaired balance<br>- Disproportionate anterocollis (dystonic) or contractures of hand or feet<br>- Absence of any of the common non motor features of disease<br>- Otherwise-unexplained pyramidal tract signs<br>- Bilateral symmetric parkinsonism<br>- Documentation of an alternative condition known to produce parkinsonism |
| **Disease duration components** | Present in red flags and exclusion criteria | Present in red flags and exclusion criteria | Removed |
| **Specificity/Sensitivity (%)** | 98.4/59.3 [2] | 88.5/94.5 [2] | 95.4/69.8 |

**Abbreviations:** MDS: Movement Disorder Society; PD: Parkinson's disease; y: years

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