Published in final edited form as:

Mov Disord. 2017 October ; 32(10): 1439–1446. doi:10.1002/mds.27125.

Discrepancies in a population-based incidence study of parkinsonism in Olmsted County: 1991–2010

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Abstract

Objective—To examine discrepancies between the clinical diagnosis of parkinsonism and neuropathological findings in a population-based cohort with parkinsonian disorders.

Background—The specific clinical diagnosis of parkinsonism is challenging, and definite confirmation requires neuropathological evaluation. Currently, autopsies are seldom performed, and most brain autopsies represent atypical or diagnostically unresolved cases.

Methods—We used a defined population-based incidence cohort with clinical parkinsonism (n=669) from the Rochester Epidemiology Project in Olmsted County, MN, 1991–2010. We reviewed reports of all patients who underwent neuropathologic examination at autopsy (n= 60; 9%) and applied consensus pathologic guidelines for neurodegenerative disease diagnosis.

Results—Among the 60 patients examined pathologically, the median time from the last recorded clinical diagnosis to death was 7 years (range from 2 to 17 years). Clinical-pathological concordance was found in 52 cases (86.7%), whereas 8 (13.3%) had a clinical-pathological discrepancy. Four patients with a clinical diagnosis of idiopathic Parkinson's disease had no pathological evidence of Lewy bodies or α -synucleinopathy; of these, pathological diagnoses were Alzheimer's disease (2 cases), progressive supranuclear palsy (1 case), and vascular parkinsonism (1 case). Two patients with clinical diagnoses of "dementia with Lewy bodies" and one patient with an "unspecified parkinsonism" had a pathological diagnosis of Alzheimer's disease without concomitant α -synuclein lesions. One patient with clinically diagnosed "progressive supranuclear

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Financial Disclosures

Drs. Turcano and Savica have nothing to disclose.

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Michelle M. Mielke - Statistical Analysis, design; review and critique of manuscript

Keith A. Josephs - Design and execution; review and critique of manuscript

James Bower – Conception and organization of the research project; review and critique of manuscript

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palsy" had indeterminate pathological findings without α -synuclein, A β - or tau-immunoreactive lesions at autopsy.

Conclusions—Overall, the clinical diagnoses of parkinsonian subtypes had good concordance with pathological confirmation (86.7%). However, clinical-pathological discrepancies were documented in 13.3%.

Keywords

parkinsonism; Lewy Bodies; supranuclear palsy; population-based incidence cohort

Introduction

With the aging of the population, the prevalence of neurodegenerative diseases such as Parkinson's disease (PD) and Alzheimer's disease (AD) is progressively increasing [1, 2]. The pathological hallmark of neurodegenerative diseases is the accumulation of specific abnormal proteins that serve as diagnostic markers of disease (e.g., tau, alpha-synuclein, β -amyloid). Thus the neuropathology is the final arbiter when brain pathologies are performed. Complicating this is the more recent recognition that mixed brain pathologies are common, potentially resulting in overlapping symptoms that confound a definitive diagnosis [3].

Recognizing that the neuropathological examination remains the diagnostic gold standard of parkinsonian disorders [4], we explored the accuracy of, and discrepancies between, the clinical and neuropathological diagnoses of parkinsonism, utilizing a well-established, population-based incidence cohort of patients with parkinsonism [5]. Historically, cases that underwent neuropathology evaluation in our community are the atypical parkinsonism [6]. In fact, in our cohort, only 9% of cases underwent post-mortem neuropathological examination. Our goal was to estimate the accuracy of the clinical diagnosis of parkinsonism and to assess the clinical phenotypes and characteristics of the discrepant patients in our pathological series.

Methods

Case Identification

We utilized the medical records-linkage system of the Rochester Epidemiology Project (REP) to ascertain all incident cases of parkinsonism in Olmsted County, MN, from 1991 to 2010 [6]. Details regarding the identification of cases and the clinical diagnostic criteria are reported elsewhere [5, 6]. The Mayo Clinic Institutional Review Board approved this study, and participating patients (or their legally authorized representatives) provided written consent to use medical information. In brief, the clinical diagnosis of "parkinsonism" was defined as the presence of at least two of the four cardinal signs: resting tremor, rigidity, bradykinesia, and postural instability. Among the patients who fulfilled the criteria for parkinsonism, we applied specific diagnostic criteria to classify the clinical subtypes of parkinsonism including PD [4–6], progressive supranuclear palsy (PSP) [6, 7], Lewy body dementia (DLB) [8], Parkinson's disease with dementia (PDD) [5], corticobasal syndrome (CBS) [9], multiple system atrophy (MSA) [10], vascular parkinsonism [11], and drug-induced parkinsonism [12]. Patients were clinically diagnosed with unspecified

parkinsonism when they had insufficient clinical documentation to determine the diagnosis or if they did not meet any of these clinical criteria [5]. Dementia was only considered present if the physician made that diagnosis and it was recorded in the medical records. All the cases were reviewed and received the final clinical diagnosis from a movement disorders specialist (RS) [5].

Pathological diagnosis

Among the 669 patients identified with a clinical diagnosis of parkinsonism, 60 (9%) underwent autopsy. Data on the incidence, demographic, and clinical characteristics of the different parkinsonisms are reported elsewhere [5, 12, 13]. The most recent cohort study including data about the distribution of subtypes of parkinsonism from the same area included 542 patients [5]. In addition to those, our cohort included 127 extra cases since we extended our case collections to 2010; the distribution of the different subtypes of parkinsonism in our cohort did not differ significantly from the one observed in the previous study. Neuropathological characterization of the cases was made according to published neuropathological criteria [14–18] based on the presence of the pathological proteins (α -synuclein, tau, Amyloid- β). [19]. Additional details are described below.

Lewy bodies diseases

The presence of Lewy Bodies (LBs) is a required pathological feature for the diagnosis of a Lewy body spectrum disorder (PD, DLB, and PDD) [20–22]. According to the initial consensus pathologic guidelines, we used the anatomical distribution of LBs to differentiate brainstem predominant (PD), limbic/transitional, and neocortical types (DLB) [15].

Tauopathies

Tau protein belongs to the family of microtubule-associated proteins, and it is typically expressed in healthy human neurons [23] but also in oligodendrocytes and astrocytes [24, 25], where it becomes particularly important under pathological conditions. The 4-repeated (4R) isoform of tau accumulates in astrocytes (“tufted astrocytes”) and in oligodendroglia (“coiled bodies”) in PSP, while astrocytic plaques and ballooned neurons are hallmarks of corticobasal degeneration (CBD) [26]. Neuronal accumulation of hyper-phosphorylated tau characterizes neurofibrillary pathological features of AD [27, 28] and primary age-related tauopathy (PART) [29].

Alzheimer disease

We used the presence of cerebral senile plaques (SP) and neurofibrillary tangles (NFT) to confirm the diagnosis of AD utilizing all 3 pathological criteria commonly used to assess the diagnosis of AD: Braak criteria [30], Consortium to Establish a Registry for Alzheimer’s Disease criterion (CERAD) [31], and the National Institute of the Alzheimer’s Association (NIA-RIA) criterion [14].

Statistical analysis

We ascertained the clinical diagnosis by reviewing clinical records of each patient with focus on the last clinical diagnosis made by a movement disorders specialist (RS) and recorded in

the medical records. Then we compared the clinical diagnosis with the pathological diagnosis by the neuropathologist. The pathological diagnosis was considered the “gold standard” to determine the final diagnosis for each patient. The diagnostic measures, including sensitivity, positive predictive value (PPV), and accuracy, were calculated.

Results

We previously identified 669 incident cases of parkinsonism in Olmsted County, MN, from 1991 to 2010 [5]. Among these 669 cases, 60 (9%) underwent autopsy. Compared to patients who did not undergo autopsy, autopsied patients did not differ with regards to sex, age at diagnosis, or age at death (all $p>0.05$). The median age at death for these 60 autopsied patients was 83 years (range: 56 to 99 years), and the median time from the last clinical diagnosis recorded in the medical records to death was 7 years (range: 2 to 17 years). The median time between the last neurological visit and death was 1.8 years (range: 1 month to 13 years). The median Hoehn & Yahr scale score at the final visit prior to death was 4 (range: 2 to 5).

Clinical-Pathological agreement

The sensitivity for the whole group of patients with a pathological confirmation of LB-related diseases (PD and DLB) clinically diagnosed correctly was 100%. PPV was 84.1%, and diagnostic accuracy was 88.3%. When we excluded from this group the three cases with a clinical diagnosis of unspecified parkinsonism, we reported a PPV of 85.7%, a sensitivity of 100%, and a diagnostic accuracy of 89.5%; we observed no false negative cases. For the clinical diagnosis of PD, PPV was 83.3% (20 out of 24), sensitivity 100%, and accuracy 93.0%. For the clinical diagnosis of DLB, PPV was 88.9% (16 out of 18), sensitivity was 100%, and the accuracy was 96.5%. The PPV for clinical diagnosis of MSA was 100% (5 out of 5), 75% for PSP (3 out of 4), and 100% for CBD (1 out of 1).

Clinical-Pathological characteristics

Of the 60 parkinsonian patients who underwent autopsy, 37 (61.7%) patients had a pathological diagnosis of a Lewy Body spectrum disorder (LBD); five (8.3%) had a pathological diagnosis of MSA; four patients (6.7%) had a pathological diagnosis of PSP; five (8.3%) had a pathological diagnosis of vascular parkinsonism. In addition, 5 (8.3%) patients had a pathological diagnosis of AD, 1 (1.6%) of CBD, 1 (1.6%) of PART, and 1 (1.6%) unspecified pathological diagnosis. We also observed 1 (1.6%) case with no pathological findings but a clinical diagnosis of drug-induced parkinsonism.

Among the 37 patients with a pathological diagnosis of LBD, 16 (43.2%) were clinically diagnosed as DLB, 20 (54.1%) with PD, and one with unspecified parkinsonism. Among the LBD cases, 25 (67.6%) had neocortical-type LBD, 11 had limbic type, and 1 was brainstem predominant. Of the 25 patients with neocortical LBD, 15 (60.0%) had hallucinations, and 19 (76.0%) had a clinical diagnosis of dementia. Of the 11 patients with limbic-type LBD, 3 (27.2%) had hallucinations and 5 (45.5%) had dementia. Of the 37 patients with a pathological diagnosis of LBD, 30 patients (81.0%) were treated with L-Dopa or dopamine

agonists, 19 (63.3%) of which showed a well-documented response to the therapy. Five (16.6%) had clinically documented dysautonomia (orthostatic hypotension).

There were five pathological cases of MSA, and all had a concordant clinical diagnosis. Of the 5 patients with MSA, none had documented L-Dopa responsiveness, 2 had ataxia, and 2 had mild upward gaze limitations.

One patient had a clinical and pathological diagnosis of CBS/CBD with clinical characteristics consistent with the diagnosis of CBS (parkinsonian symptoms with bilateral involvement, visual and auditory hallucinations, paranoia, and dementia, asymmetrical reflexes, dysexecutive dysfunction, normal eyes movement, prominent grasp reflexes and unilateral apraxia).

PSP was pathologically diagnosed in 4 cases. One patient had both PSP and LBD limbic predominant type and was clinically diagnosed with PSP. Two patients had a clinical diagnosis of PSP (1 of which also had comorbid LBD limbic predominant type pathology), 1 had PD, and 1 had unspecified parkinsonism. Among these 4 patients, one showed upward gaze limitations, one showed a skew deviation with diplopia (both vertical and horizontal), one had an eyelid apraxia without gaze limitation, and one patient had both upward and downward gaze limitations. The two patients with a concordant clinical-pathological diagnosis of PSP also reported frequent falls and a poor response to L-Dopa.

Five patients had a pathological diagnosis of vascular parkinsonism. Four (80%) of these patients had a clinical-pathological correspondence for the diagnosis, whereas one case was clinically diagnosed with idiopathic PD. In all these cases, there was clear documentation of rapid-onset symptoms after a documented acute cerebrovascular event and a step-wise progression. One case showed only mild pigmentary incontinence of the substantia nigra (sn).

Five patients had a pathological diagnosis of AD without a corresponding clinical diagnosis (clinical diagnoses: 2 DLB, 2 PD, 1 unspecified parkinsonism). All five had dementia and showed parkinsonian symptoms, but only one responded to L-Dopa.

We observed a case with a pathological diagnosis of LBD, showing a 9-year disease duration and clinical findings of dementia, upward gaze limitations, and bilateral rest tremor; one had a pathological diagnosis of advanced AD with dementia, bilateral resting tremor, cogwheel rigidity, and bradykinesia; one had a pathological diagnosis of PSP, showing a bilateral tremor at rest, right-sided bradykinesia and rigidity, skew deviation of the eyes with diplopia, and reduced abduction. In all these cases, the given clinical diagnosis was unspecified parkinsonism. In addition, there was one case of PART with a clinical diagnosis of unspecified parkinsonism and one case with unspecified pathological diagnosis with a clinical diagnosis of PSP. Only one patient was clinically diagnosed with drug-induced parkinsonism due to the previous administration of antipsychotic drugs (trifluoperazine and risperidone).

The clinical-pathological characteristics of the 52 concordant cases are reported in Table No. 1.

Discrepancies

Among 60 patients that underwent autopsy, 8 cases (13.3%) had a clinical-pathological discrepancy. The median time from diagnosis to death was 5 years (range: 2 to 9 years). The clinical and pathological characteristics of the eight discrepant cases are reported in Table 2. All the clinical diagnoses were confirmed by a movement disorders specialist (RS), who reviewed the entire medical record of each patient. Four of the eight had a clinical diagnosis of PD; none had the pathological presence of LBs or α -synuclein.

Case no. 1 had a clinical diagnosis of Parkinson's disease (PD) that responded to L-Dopa treatment. The pathological diagnosis was vascular parkinsonism with only mild pigmentary incontinence of sn and diffuse neocortical and subcortical β -amyloid plaques. No head MRI was performed for this patient. The head CT scan done at the time of the initial diagnosis revealed only physiologic calcifications within the basal ganglia and a small lacuna involving the genu of the left internal capsule.

Case no. 2 had a clinical diagnosis of PD with mild cognitive impairment whereas the pathological diagnosis was AD, with mild pigmentary incontinence of sn and cortical and subcortical diffuse β -amyloid deposits.

Case no. 3 had a clinical diagnosis of PD without the presence of any atypical features. The pathological exam showed only mild pallor of sn; β -amyloid plaques in the entorhinal cortex, subiculum, hippocampus and in the endplate; tau deposits in many structures as well as sn, subthalamic nucleus, globus pallidus (GP), cerebellar dentate nucleus, and neocortical areas. Pathological diagnosis of PSP was given for this patient.

For **Case no. 4**, the clinical diagnosis was PD without cognitive impairment, and the pathological diagnosis was AD with frequent cortical and subcortical neuritic plaques and NFT and only mild pigmentary incontinence of sn without significant neuronal loss or gliosis.

For **Cases no. 5 and 6**, the clinical diagnosis was DLB, but no LBs or α -synuclein deposits were found during the autopsy. Pathological diagnosis was AD for both (Braak stage VI; NIA-RIA criterion: high likelihood) with the presence of diffuse cortical and subcortical β -plaques and NFT. Both of them had mild pigmentary incontinence with no significant neuronal loss in sn and locus coeruleus (lc).

Case no. 7 had a clinical diagnosis of PSP but an indeterminate pathological diagnosis. There was no evidence of α -synuclein, tau or β -amyloid deposits, but interestingly the patient had clinical features of dementia, supranuclear gaze limitations, and signs of dysautonomia (urinary incontinence). In addition, there were other parkinsonian features likely caused by the administration of trifluoperazine for a concurrent diagnosis of bipolar disorder type I (bilateral resting tremor, frequent falls, and rigidity).

Case no. 8 had a clinical diagnosis of unspecified parkinsonism with a pathological diagnosis of AD, no LBs, and only non-specific α -synuclein deposits limited to the amygdala.

Discussion

In the current era, brain autopsies have become infrequent, as evidenced by the 9% frequency in this population-based cohort. This is further reduced from the 17% brain autopsy frequency among cases of parkinsonism in our community in the 15 years prior to the current study interval [6]. As previously documented [6], historically usually only individuals who donate their bodies or brains for research or who have atypical features undergo autopsy. However, in our series, the vast majority had a clinical diagnosis of LBD (20 cases clinically diagnosed as PD and 16 as DLB); thus, this general observation is not entirely true in our cohort, where we have a larger number of cases with PD and DLB. In our study, the final clinical diagnoses were consistent with the neuropathology approximately 87% of the time. We observed a high PPV for all patients with clinical diagnosis of DLB (PD plus DLB) of 85.7% and an accuracy of 89.5% for all patients with clinical diagnosis of DLB (PD plus DLB) with a sensitivity of 100%. This suggests that the advances in imaging, other testing and improved clinical criteria in the current era better equip clinicians to identify the underlying pathology and make a correct diagnosis. In the past, a number of studies investigated the accuracy of clinical diagnosis of idiopathic PD and reported an accuracy of about 76% and 84% [32–34]. The advent of the United Kingdom Parkinson's Disease Society Brain Research Center (UKPDSBRC) Clinical Diagnostic Criteria for Idiopathic PD [35] provided an additional improvement of the clinic pathology concordance, showing an overall PPV of 85.3% for clinical diagnosis of parkinsonian syndromes, a PPV of 98.6% just for clinical diagnosis of idiopathic PD with a sensitivity of 91.1%. Most of these studies were based on a clinical series of tertiary centers; thus, they may be not representative of the general population of parkinsonism. In fact, even the UKPDSBRC are devoted to define only PD; however, little is known about the whole spectrum of parkinsonism; a recent study investigating the accuracy of the clinical diagnosis of MSA reported a diagnostic accuracy of 62% [36].

Our previous study using data of 364 incident cases of parkinsonism, reported a diagnostic sensitivity of 43.7% and an accuracy of 61.5% [6]. A recent meta-analysis reported that the accuracy of the clinical diagnosis of PD in the last 25 years has remained sub-optimal [37].

The accumulation of a certain protein in specific areas of the brain is necessary for the definite diagnosis of most neurodegenerative diseases. The presence of LBs in brain, with α -synuclein as the major component, is the hallmark for the definite diagnosis of PD and DLB [20–22]. Further arguments in favor of α -synuclein accumulation as a marker of PD are due to the link between a mutation in SNCA gene encoding for α -synuclein and the subsequent development of early-onset PD in familial cases [38].

On the other hand, the presence of LBs in brain autopsies to confirm the diagnosis of PD has been recently questioned [33]. Although LBs are found in over 90% of patients with clinical diagnosis of PD in life [35], they may not be present in certain genetic forms of PD; most cases of Parkinson's gene mutations [39–42] do not seem to have LB deposition [43–46].

In our study, we reported an overall accuracy of 89.5% for the clinical diagnosis of LB-related diseases; in all these cases, the clinical diagnosis was confirmed pathologically by

the presence of LBs in specific areas of the brain. At the same time, some cases had a clinical diagnosis not supported by the pathological features. These findings suggest that LBs and α -synuclein deposition play a major role in neurodegenerative processes but are not sufficient to explain all cases. The clinical diagnoses in our cases were supported by the criteria, and there was no major evidence of atypical clinical features to change the diagnosis or confuse the clinicians. At times, the L-Dopa was untreated because of the different clinical approaches adopted by the treating neurologist or per patient decision.

We hypothesized that other mechanisms account for patients with clinical features of parkinsonism and no LB deposits. Parkinsonism may in fact represent a group of disorders with different primary mechanisms; LB deposits may be the main mechanisms of the process, but other mechanisms may lead to the same outcomes from different biochemical patterns [47]. One of these mechanisms may be related to the known vulnerability of the dopaminergic neurons of the sn to mitochondrial insults [48].

Interestingly, deposits of NFTs in the sn may theoretically lead to the same clinical syndromes using a different protein-related process. In fact, five of our cases had pathology findings consistent with AD without having the symptoms associated to the clinical diagnosis of AD. Moreover Case no. 8 in our series had a clinical diagnosis of unspecified parkinsonism and a pathologically confirmed diagnosis of advanced AD with widespread neocortical β -amyloid plaques and NFT but only non-specific α -synuclein deposits limited to amygdala. This patient showed clinical features of dementia and parkinsonian symptoms but, interestingly, no visual hallucinations [49]. Amygdala LBs are not uncommon in AD [50], but the clinical significance of these findings is unknown. On the other hand, it is also possible that age-related parkinsonism plays a role in some of the cases with discrepant clinical-pathologic features [51, 52].

Furthermore, AD pathology coexists in DLB patients [53] (~87 % [54]). In contrast, AD pathology is only present in ~40% of PD patients [55]. Among the 37 pathologically confirmed DLB cases, we found 32 cases (86.5%) with diffuse β -amyloid plaques. These findings suggest frequent coexistence of these two diseases and maybe a common role for β -amyloid plaques and LBs in the development of dementia in DLB. The accumulation of LBs in LB-related disorders is not sufficient to explain the developing of dementia in all the cases, since some PD patients with a high neocortical LB burden remain cognitively intact [56]. Co-occurrence of β -amyloid plaques and LBs is associated with a higher cognitive impairment [57] and it is a better predictor of dementia compared with the accumulation of LBs or β -amyloid alone [56]; DLB patients who show the presence of β -amyloid deposition tend to develop a higher rate of brain atrophy with an AD-like pattern[57]; moreover a recent study reported that increasing severity of AD neuropathology in patients with LB-related diseases may lead to a narrower interval between the onset of motor symptoms and the development of dementia [58]. In light of these findings we explored our cohort and among the 32 patients with β -amyloid in the brain autopsy, 18 (56.3%) were clinically diagnosed as demented. The median time between the onset of motor symptoms and the development of clinically diagnosed dementia was 1 year (range from 0 to 7 years). One patient with a long clinical history of PD developed dementia after 14 years from the onset

of the disease; the presence of AD neuropathological changes was described as “pathologic aging”.

Although the neuropathological examination is still required for the definite diagnosis of neurodegenerative diseases, a number of factors can contribute to the results of pathology: aging of the population, overlapping symptoms shared by different disorders, extreme heterogeneity of some neurological diseases and the well established presence of mixed pathology mostly in the late stages of the disease. In addition, the relatively low referral rate of patients with parkinsonism that come to autopsy and the possible different pathophysiological mechanisms underlining these diseases raise doubts as to whether the brain autopsy should be considered as the gold standard for the diagnosis of LB-related diseases. The lack of correlation between the pathological findings and clinical features in some cases referred to as incidental Lewy Body disease, further underline the importance of developing specific in vivo biomarkers not to incur in the complexity of some cases.

Our study has a number of strengths. First, we utilized the records-linked system of the REP to study a large, well-defined, population-based cohort of parkinsonism (669 patients). All of the medical facilities in Olmsted County, MN, are included in the REP, and it is unlikely that Olmsted County patients would have been evaluated for parkinsonism at medical facilities outside the county. Second, the population-based nature of this series makes this study an improvement over other referral-based studies that suffer from patient- and autopsy-selection biases. Third, the median follow-up of 7 years from clinical diagnosis to death allowed us to strengthen our clinical diagnosis and to categorize every patient by type of parkinsonism. Fourth, the agreement between autopsy findings and clinical diagnoses was high, suggesting that the clinical diagnosis made by the physicians was accurate. Lastly, all the autopsies were performed by the same group of board-certified neuropathologists, who have long-standing training in the pathological diagnosis of these diseases.

Our study also has a number of limitations. First, given the small number of patients who underwent autopsy, we caution against over-interpreting our data. Second, most patients were seen by several physicians at different times, and the clinical findings were recorded as part of the routine clinical practice and not standardized for research. Therefore, we may have missed features that were not documented. Third, we had few patients with a clinical or pathological diagnosis of PSP, MSA, and CBD. Fourth, despite not having observed differences between the patients who underwent autopsy with the patients who did not, the subjects (or their legally authorized representatives) who agreed to donate their brains may have been at higher risk for an atypical or more severe disease; thus, we cannot completely exclude a referral bias.

In conclusion, the linear concept that parkinsonism and other neurodegenerative diseases are only due to the accumulation of a certain protein in the brain cells is somehow incomplete; in fact, rare cases of parkinsonian syndrome may be associated with an unexpected series of protein deposition. Interestingly, we observed an overall good accuracy for the clinical diagnosis of parkinsonian syndrome; however, pathological confirmation is still necessary for the definitive diagnosis. Differential diagnoses between parkinsonisms still represent a challenge for physicians because of overlapping clinical and pathological characteristics,

especially in the elderly. Improving the diagnostic accuracy of parkinsonisms can lead to better therapeutic decisions, prognosis, and outcomes for the patients.

Acknowledgments

Dr. Mielke receives funding from the National Institutes of Health, the Michael J. Fox Foundation, and unrestricted research grants from Biogen. She has consulted for Lysosomal Therapeutics, Inc. Dr. Parisi receives funding from the National Institute of Neurological Disorders and Stroke and Novartis Pharmaceuticals. Dr. Bower receives funding from the Parkinson's Disease Foundation, Inc. Dr. Josephs receives funding from the National Institute on Aging, the National Institute of Neurological Disorders and Stroke, and the National Institute on Deafness and Other Communication Disorders. Dr. Boeve receives funding from the National Institute on Aging, the National Institute of Neurological Disorders and Stroke, Roivant Sciences, C2N Diagnostics, and Axovant Sciences.

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Table No. 1

Clinical-pathological characteristics of the 52 concordant cases in our study.

Clinical Dx (%) Tot=52	Pathological Dx
PD=20 (38.5%)	LBD
DLB=16 (30.8%)	LBD
MSA=5 (9.6%)	MSA
Vascular Parkinsonism=4 (7.7%)	Vascular parkinsonism
	LBD=1
Unspecified parkinsonism=3 (5.8%)	PSP=1
	PART=1
PSP=2 (3.8%)	PSP
CBS=1 (1.9%)	CBD
DIP=1 (1.9%)	No pathological findings

Abbreviations: PD, Parkinson's disease; DLB, dementia with Lewy bodies; LBD, Lewy body disorder; PSP, progressive supranuclear palsy; AD, Alzheimer disease; MSA, multiple system atrophy; CBD, corticobasal degeneration; CBS, corticobasal syndrome; PART, primary age-related tauopathy; DIP, drug-induced parkinsonism; Dx, diagnosis.

Table No. 2

Clinical-pathological characteristics of the 8 discrepant cases in our study.

Case No.	Clinical dx	Pathological dx	Resting tremor	Bradykinesia	Rigidity	Dementia	UPDRS III (max 108)	Age of death (years)	Time from clinical dx to death (months)	L-Dopa response
1	PD	Vascular parkinsonism	Yes	Yes	Yes	No	21	89	27	Yes
2	PD	AD	No	No	Yes	Yes	24	82	24	No drugs administered for PD
3	PD	PSP	Yes	Yes	Yes	No	16	93	39	No drug administered for PD
4	PD	Early AD	Yes	Yes	No	No	16	95	15	No
5	DLB	Advanced AD	Yes	Yes	Yes	Yes	15	94	38	No drug administered for PD
6	DLB	Advanced AD	No	Yes	Yes	Yes	20	87	60	Yes
7	PSP	Indeterminate	Yes	No	Yes	Yes	25	58	25	N/A
8	Unspecified parkinsonism	Advanced AD	Yes	Yes	Yes	Yes	28	61	21	N/A

Abbreviations: PD, Parkinson’s disease; DLB, dementia with Lewy bodies; PSP, progressive supranuclear palsy; AD, Alzheimer disease; UPDRS III, unified Parkinson’s disease rating scale part III.