Low clinical diagnostic accuracy of early vs advanced Parkinson disease: Clinicopathologic study

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Clinicopathologic study

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ABSTRACT

Objectives: Determine diagnostic accuracy of a clinical diagnosis of Parkinson disease (PD) using neuropathologic diagnosis as the gold standard.

Methods: Data from the Arizona Study of Aging and Neurodegenerative Disorders were used to determine the predictive value of a clinical PD diagnosis, using 2 clinical diagnostic confidence levels, PossPD (never treated or not clearly responsive) and ProbPD (responsive to medications). Neuropathologic diagnosis was the gold standard.

Results: Based on first visit, 9 of 34 (26%) PossPD cases had neuropathologically confirmed PD while 80 of 97 (82%) ProbPD cases had confirmed PD. PD was confirmed in 8 of 15 (53%) ProbPD cases with <5 years of disease duration and 72 of 82 (88%) with ≥5 years of disease duration. Using final diagnosis at time of death, 91 of 107 (85%) ProbPD cases had confirmed PD. Clinical variables that improved diagnostic accuracy were medication response, motor fluctuations, dyskinesias, and hyposmia.

Conclusions: Using neuropathologic findings of PD as the gold standard, this study establishes the novel findings of only 26% accuracy for a clinical diagnosis of PD in untreated or not clearly responsive subjects, 53% accuracy in early PD responsive to medication (<5 years' duration), and >85% diagnostic accuracy of longer duration, medication-responsive PD. Caution is needed when interpreting clinical studies of PD, especially studies of early disease that do not have autopsy confirmation. The need for a tissue or other diagnostic biomarker is reinforced.

Classification of evidence: This study provides Class II evidence that a clinical diagnosis of PD identifies patients who will have pathologically confirmed PD with a sensitivity of 88% and specificity of 68%. *Neurology*® 2014;83:1–7

GLOSSARY

AZSAND = Arizona Study of Aging and Neurodegenerative Disorders; **MSA** = multiple system atrophy; **NPV** = negative predictive value; **ParkNOS** = parkinsonism not otherwise specified; **PD** = Parkinson disease; **PossPD** = possible PD; **PPV** = positive predictive value; **ProbPD** = probable PD; **PSP** = progressive supranuclear palsy; **UPDRS** = Unified Parkinson's Disease Rating Scale; **UPSIT** = University of Pennsylvania Smell Identification Test.

Making an accurate diagnosis of Parkinson disease (PD) is critical for patient care as well as research related to epidemiology, genetics, imaging, biomarker discovery, and both symptomatic and disease-modifying treatments. Methods for diagnosing PD are limited by the lack of a tissue diagnostic test or other definitive biomarker test. Current diagnostic criteria for PD are based on the nonspecific clinical findings of rest tremor, cogwheel rigidity, and bradykinesia,[1] but the gold standard remains to be neuropathologic confirmation.

A major goal to improve diagnostic accuracy in living patients has been to find a blood, CSF, or other tissue biomarker for PD. One inherent complicating factor for finding a biomarker in living patients with PD is the potential inaccuracy of a clinical rather than autopsy-confirmed diagnosis. Validation of an accurate diagnostic biomarker for PD may require neuropathologic confirmation of the PD diagnosis, as has been demanded for amyloid imaging in Alzheimer disease research.[2]

Editorial, page XXX

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Numerous studies report that neuropathologic confirmation of a clinical diagnosis of PD may range from 65% to 93%, depending on the criteria used and the stage of disease.[3–8] Recently, the use of dopaminergic neuroimaging has improved the diagnosis of PD in living patients, and appears to be sensitive but not specific, and has not yet been validated by postmortem examination.[9] This study presents clinical and neuropathologic data on the diagnostic accuracy of longitudinally followed subjects with PD based on disease duration, medication responsiveness, and clinical signs.

METHODS

Subjects. Subjects enrolled from 1997 to 2013 in an ongoing longitudinal clinical-neuropathologic study, the Arizona Study of Aging and Neurodegenerative Disorders (AZSAND), with autopsies performed by the Banner Sun Health Research Institute Brain and Body Donation Program (www.brainandbodydonationprogram.org), were included.

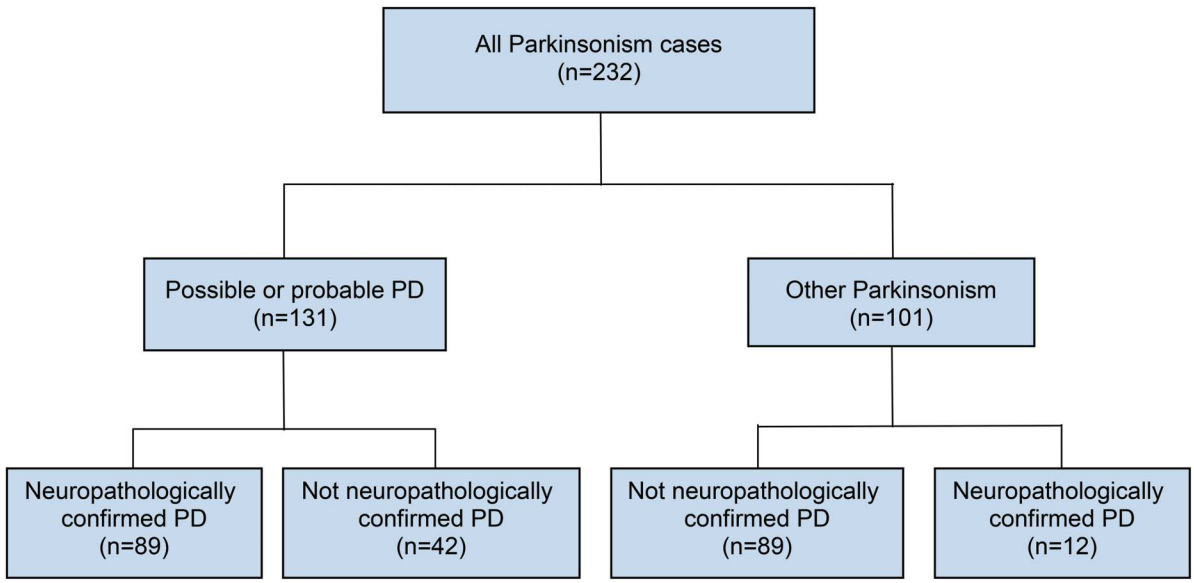
Standard protocol approvals, registrations, and patient consents. All subjects signed written informed consent approved by the Banner Sun Health Institutional Review Board.

Clinical assessments. Subjects received annual standardized movement disorder examinations by a fellowship-trained movement disorders specialist (C.A., H.S., J.C., E.D.-D.) as previously described.[10,11] Examinations included a full Unified Parkinson's Disease Rating Scale (UPDRS) (performed in the practically defined off state whenever possible),[12] medication history, and neuropsychological test battery.[11] Olfactory testing, using the University of Pennsylvania Smell Identification Test (UPSIT), began in 2005.[13,14]

At each assessment, subjects were evaluated for one or more of the cardinal signs of PD: *rest tremor*—a UPDRS motor score of ≥1 for lower lip or any limb; *bradykinesia*—a UPDRS motor score of ≥1 in 2 motor tests on the same side of the body (arm/leg) or a score of ≥2 in one motor test of a limb; and *cogwheel rigidity*—a UPDRS motor score of ≥1 of any limb. After each evaluation, subjects were given a movement disorders diagnosis: (1) probable PD (ProbPD): 2 of 3 cardinal signs, no symptomatic cause, improvement when treated with dopaminergic medications and continued response if still being treated, or if lack of current response, then an explanation for why treatment was no longer working (i.e., inadequate dose due to side effects); (2) possible PD (PossPD): 2 of 3 cardinal signs, no symptomatic cause, symptoms or signs present for ≤5 years, dopaminergic treatment had not been tried or an adequate trial had not clearly occurred (i.e., too low a dose, side effects that limited therapeutic dose, etc.); (3) progressive supranuclear palsy (PSP): meeting National Institute of Neurological Disorders and Stroke PSP clinical criteria[15] for diagnosis; (4) parkinsonism not otherwise specified (ParkNOS): parkinsonism without response to an adequate dose of dopaminergic medication or disease duration of >5 years and had not been treated or been given an adequate trial of dopaminergic treatment, or appeared to have another etiology including an unclear neurodegenerative condition, dementia with parkinsonian features, or secondary parkinsonism; or (5) multiple system atrophy (MSA): autonomic dysfunction with or without parkinsonism poorly responsive to medication and/or cerebellar findings. At the time of death, all available medical records were reviewed and a final clinical diagnosis was given.

Neuropathologic assessments. The postmortem diagnosis of PD was made based on previously reported neuropathologic criteria together with a clinical diagnosis of parkinsonism.[16–19] This included subjects with a clinical diagnosis of ProbPD, PossPD, or parkinsonism with neuropathologic evidence of substantia nigra pigmented neuron loss and Lewy bodies. Gross and microscopic neuropathologic assessments were made by a single observer (T.B.) initially blinded to clinical history or clinical diagnosis, then able to review clinical information to make an appropriate clinical-neuropathologic diagnosis. Paraffin sections of the substantia nigra were stained immunohistochemically using a polyclonal antibody raised against an α-synuclein peptide fragment phosphorylated at serine 129, after epitope exposure with proteinase K, to identify Lewy bodies.[17,20–23]

Figure Flow diagram



PD = Parkinson disease.

Histologic evaluation of substantia nigra pigmented neuron loss was graded using hematoxylin & eosin–stained microscopic sections.[17]

Statistical analysis. Diagnostic accuracy was assessed for the clinical diagnosis at the first visit and for the final clinical diagnosis. The sample included all subjects with ProbPD, PossPD, or other types of parkinsonism at the given time point. Positive predictive value (PPV) was the percentage of subjects with neuropathologically confirmed PD among those with the given clinical diagnosis. Negative predictive value (NPV) was the percentage of subjects without neuropathologically confirmed PD among those with other forms of parkinsonism. Sensitivity was the percentage of subjects with a clinical diagnosis of PD among those with neuropathologically confirmed PD, and specificity was the percentage of subjects without PD among those without neuropathologically confirmed PD. Mean UPSIT scores were compared between groups by using the 2-sample t test. UPSIT cutoff scores were chosen in order to maximize the Youden index (sensitivity + specificity − 1). Proportions were compared among groups by using the Pearson χ^2 test. The Fisher exact test was used instead of the Pearson χ^2 test if the minimum expected cell count was less than 5. The primary research question was to determine the diagnostic accuracy of a clinical diagnosis of PossPD or ProbPD using neuropathologic assessment as the reference standard, and the level of evidence was Class II.

RESULTS

Demographics. At the time of first visit, there were 232 cases of parkinsonism, 97 subjects had ProbPD, 34 PossPD, and 101 had other types of parkinsonism (ParkNOS, PSP, MSA) (figure). Age, sex, and disease duration at first visit and time of death are presented in table 1. When ProbPD was subdivided by disease duration, those with disease duration less than 5 years had an older age of disease onset (mean 76.0 years) than those with disease duration of at least 5 years (mean 64.0 years), although age at death was no different. The PossPD cases had shorter disease duration (mean 0.7 years) at first visit, but somewhat older age at onset (80.6 years) and age at death (87.5 years).

Predictive value for a diagnosis of PossPD. For the 34 subjects with PossPD (31 never treated and 3 with an inadequate treatment trial) at the first visit, only

Table 1 Demographics for subjects with parkinsonism followed to autopsy and percentage with a neuropathologically confirmed diagnosis of PD

	PossPD[a]	ProbPD[b]	ProbPD[b] <5 y	ProbPD[b] ≥5 y	Other parkinsonism[c]
First visit					
No.	34	97	15	82	101
Female, n (%)	13 (38)	32 (33)	4 (27)	28 (34)	43 (43)
Age at visit, y, mean (SD)	81.4 (7.2)	76.8 (7.5)	78.4 (6.7)	76.6 (7.7)	80.6 (6.9)
Age at symptom onset, y, mean (SD)	80.6 (7.6)	65.8 (10.2)	76.0 (6.8)	64.0 (9.6)	NA
Age at death, y, mean (SD)	87.5 (6.3)	80.6 (7.0)	82.4 (6.0)	80.3 (7.1)	83.2 (6.8)
Duration of PD symptoms at visit, y, mean (SD)	0.7 (1.6)	11.0 (6.6)	2.4 (1.2)	12.6 (6.0)	NA
Duration between visit and death, y, mean (SD)	6.1 (3.4)	3.8 (2.9)	4.1 (3.1)	3.7 (2.9)	2.6 (2.1)
Duration of PD symptoms at death, y, mean (SD)	6.8 (3.6)	14.8 (6.9)	6.4 (3.4)	16.3 (6.3)	NA
Neuropathologically confirmed PD, n (%)	9 (26)	80 (82)	8 (53)	72 (88)	12 (12)
95% CI, %	13-44	73-89	27-79	79-94	6-20
Final clinical diagnosis					
No.	15	107	4	103	141
Female, n (%)	5 (33)	36 (34)	2 (50)	34 (33)	65 (46)
Age at PD symptom onset, y, mean (SD)	85.4 (5.3)	67.2 (10.3)	80.6 (8.3)	66.7 (10.0)	NA
Age at death, y, mean (SD)	88.7 (5.2)	81.0 (6.8)	83.0 (7.5)	80.9 (6.8)	84.2 (7.3)
Duration of PD symptoms at death, y, mean (SD)	3.3 (2.5)	13.7 (6.8)	2.38 (0.89)	14.2 (6.5)	NA
No. of visits, mean (SD), min-max	2.3 (1.3), 1-5	2.8 (2.0), 1-8	2.00 (0.82), 1-3	2.9 (1.0), 1-8	2.4 (1.8), 1-10
Neuropathologically confirmed PD, n (%)	3 (20)	91 (85)	4 (100)	87 (84)	12 (9)
95% CI, %	4-48	77-91	40-100	76-91	4-14

Abbreviations: CI = confidence interval; max = maximum; min = minimum; NA = not applicable; PD = Parkinson disease; PossPD = possible PD; ProbPD = probable PD.
Data are presented for the clinical diagnosis at the first assessment and at the final assessment before death. The ProbPD group is subdivided based on disease duration of <5 or ≥5 years.
[a] PossPD defined as 2 of the 3 cardinal signs, no symptomatic cause, symptoms or signs were present for ≤5 years, dopaminergic treatment had not been tried or an adequate trial had not clearly occurred.
[b] ProbPD defined as 2 of the 3 cardinal signs, no symptomatic cause, a response to dopaminergic medications and continued response if still being treated, or if lack of current response then an explanation for why treatment was no longer working.
[c] Parkinsonism not otherwise specified, progressive supranuclear palsy, dementia with Lewy bodies, multiple system atrophy, or corticobasal degeneration.

9 had neuropathologically confirmed PD (PPV 26%, table 1). The sample size was too small to determine whether specific clinical signs improved diagnostic accuracy.

Predictive value for ProbPD. For the 15 subjects with ProbPD who had disease duration of less than 5 years at first visit, only 8 had neuropathologically confirmed PD (PPV 53%, table 1). In subjects with ProbPD who had disease duration of at least 5 years, 72 of 82 (PPV 88%) had neuropathologically confirmed PD. Using a final clinical diagnosis of ProbPD at the time of death, the PPV was 84% (87/103) for disease duration of at least 5 years and 100% (4/4) for disease duration of less than 5 years.

Predictive value based on clinical signs. Because response to dopaminergic medication is the key differentiating factor between ProbPD and PossPD, this was the key clinical finding that improved diagnostic accuracy (table 1). Rest tremor was not associated with autopsy confirmation of PD among subjects with either PossPD or ProbPD. Among subjects with PossPD, 6 of 28 subjects with rest tremor had PD vs 3 of 6 without rest tremor, while among subjects with ProbPD, 42 of 51 subjects with rest tremor had PD vs 35 of 43 without rest tremor. Because only 15 cases had ProbPD short duration, the comparison for rest tremor was not performed.

Requiring all 3 cardinal features (bradykinesia, rest tremor, and rigidity) at first visit, 5 of 12 (42%) PossPD cases had confirmed PD while 4 of 22 (18%) cases without all 3 signs had PD ($p = 0.22$). For ProbPD cases with 3 signs, 36 of 40 (90%) had PD while 41 of 54 (76%) without all 3 signs had PD ($p = 0.08$). Asymmetric onset also did not improve PPV (data not shown).

For the ProbPD group, the percentage with autopsy-confirmed PD differed ($p = 0.006$) if the subjects had motor fluctuations (47/51 [92%]) vs no motor fluctuations (31/44 [70%]) or dyskinesia (27/28 [96%] with and 50/66 [76%] without dyskinesia, $p = 0.02$). Because there were only 15 cases of ProbPD with disease duration less than 5 years, identifying key clinical factors that would increase diagnostic accuracy was not possible.

Olfactory testing and diagnostic accuracy. Of the 16 PossPD cases tested at first visit, the mean UPSIT score for the 4 cases with autopsy-confirmed PD was 13.5, and the mean UPSIT score was 29.2 for the 12 who did not have PD ($p < 0.001$) (table 2). Using a cutoff score of 22, 3 of 4 (75%) PossPD cases with UPSIT <22 had PD and 1 of 12 (8%) of those with a score of ≥22 had PD ($p = 0.03$).

Of ProbPD cases with UPSIT testing at first visit, those with neuropathologically confirmed PD had significantly lower UPSIT scores ($p < 0.001$) (table 2). Using an UPSIT cutoff score of 20, 89% of the ProbPD cases with a score <20 had pathologically confirmed PD while 33% of cases with an UPSIT ≥20 had PD ($p = 0.02$). Data for ProbPD cases at the time of autopsy also revealed significant hyposmia in those with neuropathologically confirmed PD (table 2).

Subjects with ProbPD without neuropathologically confirmed PD. Sixteen ProbPD cases at the time of death did not have neuropathologically confirmed PD (table 3). Mean age at symptom onset and death was higher than the neuropathologically confirmed PD group (tables 1 and 3). Seven had PSP with or without other neuropathologic findings, 6 had various neurodegenerative findings, and 3 had no clear neuropathologic findings to explain the parkinsonism, and they did not have drug-induced parkinsonism. One case of PSP had Lewy bodies but not in the substantia nigra.

Sensitivity and specificity: Clinical diagnosis in pathologically proven PD. There were 106 subjects with a final clinical-neuropathologic diagnosis of PD (table 4). The sensitivity for the clinical diagnosis of ProbPD was 91 of 106 (86%). There were 5 cases clinically diagnosed with PSP who had a neuropathologic diagnosis of PD. Seven cases with a final clinical diagnosis of ParkNOS met neuropathologic criteria for PD. Some had ProbPD or PossPD at an earlier visit, but before their death, the clinical diagnosis was changed to ParkNOS by the examiner.

The specificity of a final clinical diagnosis without ProbPD was 90% because only 16 of 157 subjects

Table 2 UPSIT scores for subjects who did and did not have neuropathologically confirmed PD

	Neuropathologic diagnosis		
	PD	Not PD	*p*
ProbPD at first visit			
No.	19	6	
UPSIT, mean (SD)	14.6 (4.4)	24.7 (6.9)	<0.001
UPSIT <20, n (%)	17 (89)	2 (33)	0.02
ProbPD at death			
No.	24	5	
UPSIT, mean (SD)	14.8 (5.0)	23.6 (7.7)	0.003
UPSIT <26, n (%)	23 (96)	2 (40)	0.01
PossPD at first visit			
No.	4	12	
UPSIT, mean (SD)	13.5 (7.2)	29.2 (5.2)	<0.001
UPSIT <22, n (%)	3 (75)	1 (8)	0.03

Abbreviations: PD = Parkinson disease; PossPD = possible PD; ProbPD = probable PD; UPSIT = University of Pennsylvania Smell Identification Test.

Table 3 Neuropathologic findings in subjects with ProbPD at death who did not have neuropathologic findings of PD at autopsy

No.	16
Female, n (%)	6 (38)
Age at symptom onset, y, mean (SD)	77.0 (7.0)
Age at death, y, mean (SD)	87.1 (6.4)
Duration of symptoms at death, y, mean (SD), min-max	10.1 (5.0), 5.3-34.6
Final clinical-neuropathologic diagnosis, n (%)	
No clear pathologic process	3 (19)
PSP, AD	3 (19)
PSP	2 (12.5)
PSP, tau	1 (5)
PSP, LTS	1 (5)
MSA	1 (5)
AD	1 (5)
AD, VaD	1 (5)
VaD	1 (5)
HS	1 (5)
Tau	1 (5)

Abbreviations: AD = Alzheimer disease; HS = hippocampal sclerosis; LTS = Lewy type synucleinopathy that did not meet neuropathologic criteria for Parkinson disease; max = maximum; min = minimum; MSA = multiple system atrophy; PD = Parkinson disease; ProbPD = probable PD; PSP = progressive supranuclear palsy; VaD = vascular dementia.

without neuropathologically confirmed PD had ProbPD (table 4).

NPV of a clinical diagnosis of other parkinsonism. Of the 101 subjects with other types of parkinsonism at the first visit, 89 did not have neuropathologically confirmed PD (NPV 88%, table 1). At autopsy, 129 of 141 cases of other types of parkinsonism did not have neuropathologically confirmed PD (NPV 91%).

Table 4 Demographics and clinical diagnoses for subjects with and without neuropathologically confirmed PD

	Neuropathologic diagnosis	
	Not PD	PD
No.	157	106
Female, n (%)	69 (44)	37 (35)
Age at PD symptom onset, y, mean (SD)	NA	66.8 (10.6)
Age at death, y, mean (SD)	84.9 (7.3)	80.5 (6.5)
Duration of PD symptoms at death, y, mean (SD)	NA	13.7 (7.1)
ProbPD, n (%) (95% CI)	16 (10) (6-16)	91 (86) (78-92)
ProbPD or PossPD, n (%)	28 (18)	94 (89)
Final clinical diagnosis, n (%)		
ProbPD	16 (10)	91 (86)
ParkNOS	108 (69)	7 (7)
PossPD	12 (8)	3 (3)
PSP	11 (7)	5 (5)
DLB	8 (5)	0 (0)
MSA	2 (2)	0 (0)

Abbreviations: CI = confidence interval; DLB = dementia with Lewy bodies; MSA = multiple system atrophy; NA = not applicable; ParkNOS = parkinsonism not otherwise specified; PD = Parkinson disease; PossPD = possible PD; ProbPD = probable PD; PSP = progressive supranuclear palsy.

DISCUSSION These data indicate that early in the course of a parkinsonian disorder, even if the subject is responsive to dopaminergic medication, the clinical diagnosis of PD may have relatively poor accuracy. For subjects who were never treated or possibly inadequately treated (PossPD), the PPV was very poor—only 26% at the time of first visit (mean symptom duration of 0.7 years). This is a critical finding given the number of studies attempting to find biomarkers or disease-modifying treatments in very early PD cases. These data improve on previously published clinical-neuropathologic correlation studies showing that appreciable numbers of subjects diagnosed with PD during life, especially those for whom signs and symptoms have been present for less than 5 years, do not have neuropathologically confirmed PD.[3,4,24]

Given the inaccuracy of the clinical diagnosis, these data are very sobering and have significant implications for studies that enroll subjects with early PD. The inaccuracy has the potential of severely compromising the likelihood of observing an adequate effect size in a trial. This inaccuracy was present despite that all cases were examined by a small group of movement disorder specialists as opposed to many neurologists and geriatricians who examined the cases in other studies.[4] For subjects responsive to medication, ProbPD, longer disease duration improved diagnostic accuracy; disease duration $\geq$5 years had PPV of 88%. An unexpected finding was that the PPV was only 53% for ProbPD cases with <5 years' disease duration at first visit. A disease duration of >5 years was also found to be key to making the correct clinical diagnosis in an earlier study.[3] In that study of 43 patients initially diagnosed with PD, only 28 (65%) had neuropathologically confirmed PD.[3] After a mean follow-up period of 12 years, 41 still had a clinical diagnosis of PD at the final visit before death, but only 31 (76%) had PD pathologically.[3]

In a study of 100 cases,[4] 76 subjects with PD had neuropathologically confirmed PD. The study did not assess neuropathologic diagnosis in longitudinally followed subjects with early, untreated PD. Retrospective application of diagnostic criteria[7] (presence of bradykinesia plus other factors including asymmetry, rest tremor, progression, response to levodopa, >5 years' response + dyskinesias, >10 years' disease course) improved the accuracy to 82% (73/89).[25] The best predictors of pathologically proven PD were no atypical features of PD, an asymmetric onset, and no suggestion of a cause for another parkinsonian syndrome.[25] Tremor-predominant disease had a 91% PPV, but it is critical to note that tremor was only present in 11 (14%) of their 76 cases, so

that these investigators concluded that this may therefore have occurred by chance.[25] The current data did not show improved PPV for ProbPD cases with rest tremor or with asymmetry at first visit. If all 3 cardinal signs were present, the PPV was 90% in the present study, and 88% to 92% in other studies.[6,25] However, the current data did not show that having all 3 cardinal signs significantly differed from not having all of them.

The present data clearly showed that medication response improved PPV, as did the presence of motor fluctuations (92% PPV at first visit) or dyskinesia (96% PPV at first visit). That is not surprising because fluctuations and dyskinesia help to determine responsiveness to dopaminergic medication. However, in subjects responsive to dopaminergic medications but having disease duration <5 years, the PPV was only 53%. While sample size was small (n = 15), this finding supports the clinical and pathologic finding that subjects with other forms of parkinsonism may respond to dopaminergic medications early in the disease course.[26]

Hyposmia has been linked to PD,[13,14] and while the study sample was small, this study demonstrates that low UPSIT scores significantly improve the PPV. The value of the UPSIT may be greatest in early disease duration cases, especially in cases with PossPD because 3 of 4 PossPD subjects with an UPSIT <22 had PD while only 1 of 12 with a score ≥22 had PD. As AZSAND, PARS,[27] PPMI,[28] and PRIPS[29,30] continue, the issue of using hyposmia as an inclusion criterion for early PD studies will become clearer.

It was not surprising that many false-positive cases had a neuropathologic diagnosis of PSP or another neurodegenerative disorder. Most had a lack of response to dopaminergic medication or the loss of response to these medications while followed during life. In one study, 6 of 24 clinically diagnosed PD cases had PSP and 5 had MSA,[4] and in a second study of 10 cases without pathologic PD, 6 had MSA and 2 had PSP.[6] As for the false-negative rate of diagnostic criteria, previous studies found that approximately one-third of cases with pathologically confirmed PD were not clinically diagnosed as PD[4,5,25,31] compared with the present study of only 10% for ProbPD.

One limitation of this study was the age of the PossPD cases. The mean age of disease onset for the ProbPD group was 67 years, and mean age at death was 80 years, suggesting the ProbPD cases are similar to those reported in other studies,[32,33] including one discussed above[25] (PD onset 64.5 years, age at death 76.5 years). However, the PossPD group had a mean age at onset of 80.6 years and a mean age at death of 87.5 years. Whether a diagnosis of PossPD in a younger cohort would have a similar poor PPV cannot be determined from AZSAND data. It is possible that some of these cases had bradykinesia related to other medical issues, such as arthritis (although the examining physician takes this into account), or that the research diagnosis of PossPD was too lenient, as suggested by the lower degree of certainty for having PD.

Thus, the diagnostic accuracy of a clinical diagnosis of PD (both PossPD and ProbPD) at first visit varies between 26% and 88%, with shorter duration of disease and subjects without a clear response to dopaminergic medication having markedly lower diagnostic accuracy. As clinical research studies attempt to find the earliest possible biomarkers for PD and early, disease-modifying treatments for PD, the low diagnostic accuracy at this stage needs to be addressed and will continue to be a critical impediment until autopsy- or biopsy-verified diagnostic biomarkers are developed.

AUTHOR CONTRIBUTIONS

C. Adler and J. Hentz wrote the first draft of the manuscript. All authors contributed to manuscript writing/revision. Authors involved in patient recruitment and clinical activities included C. Adler, H. Shill, J. Caviness, E. Driver-Dunckley, M. Sabbagh, S. Jacobson, and C. Belden, while authors involved in postmortem tissue analysis included L. Sue, B. Dugger, and T. Beach. Statistical analysis was performed by J. Hentz.

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