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# Importance of Low Diagnostic Accuracy for Early Parkinson's Disease

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Autopsy-validated studies of clinical diagnostic accuracy in early Parkinson's disease (PD) indicate that, as compared with patients followed for a number of years, misdiagnosis is common. It is not that these individuals do not have parkinsonism (bradykinesia, cogwheel rigidity, or rest tremor), but rather the neuropathological findings do not support a diagnosis of PD, defined as loss of SN dopamine (DA) neurons in the presence of Lewy bodies. This is even true for an appreciable fraction of those with parkinsonism responding to dopaminergic medications.[1,2] Thus, making a clinical diagnosis of PD can be difficult, and we have previously reported a low diagnostic accuracy in early PD,[2] confirming an earlier study.[3] We now summarize, for the first time in the literature, the results from these two studies in combination with a third previous study[4] and provide further relevant commentary. In the three studies that included initial, early diagnosis, only 5 of 13 (38%), 28 of 43 (65%), and 8 of 15 (53%) patients clinically diagnosed with early PD were confirmed to have PD at autopsy.[2–4] Taken together, these data from three different research groups report a diagnostic accuracy of only 58% (41 of 71) for parkinsonian subjects with an initial, early diagnosis of PD.

These findings of poor diagnostic accuracy for an initial/early diagnosis of PD differ from the higher diagnostic accuracy found in autopsy studies with a final clinical diagnosis of PD following more than 10 years of follow-up and/or with retrospective reclassification of subjects after autopsy.[5–7] Unfortunately, for research or therapeutic clinical trials targeting much earlier disease states, subjects must be categorized without the benefit of years of longitudinal clinical assessments.

It is important to note that diagnostic inaccuracy has also been reported using clinical biomarkers for PD. The introduction of DA functional imaging has confirmed the presence of a worrisome misdiagnosis rate. Whereas $^{123}$I-CIT, $^{18}$F-DOPA, $^{123}$I-FP, $^{123}$I-ioflupane (DAT), and other DA functional scans are known to lack specificity for PD,[8] and hence should not be used as a single test to diagnose PD, DA scans are often used as a diagnostic adjunct. If a parkinsonian subject does not have an abnormal scan, then these subjects are

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classified as being SWEDDs (scans without evidence of DA deficit) and thus considered not likely to have PD. In a recent review, 3.6% to 19.6% of clinically presumptive PD subjects in drug or imaging studies have been found to be SWEDDs.[9]

Relevant studies of early PD have also noted substantial proportions of SWEDDs. In the PRECEPT study,[10] eligible patients were those who had, at the time of the screening and baseline evaluations, at least 2 of the cardinal signs of PD (resting tremor, bradykinesia, or rigidity) and no current or imminent PD disability requiring DA therapy. Of 799 such subjects, 91 (11.4%) had a negative $^{123}$I-CIT scan and were thus classified as SWEDDs. Similarly, in the PPMI (Parkinson Progression Markers Initiative) study,[11] which enrolled 309 subjects with early PD, 42 were SWEDDs (13.6%). In a follow-up study of nonmotor symptoms in the PPMI cohort, 62 of 412 (15%) of enrolled subjects were SWEDDs.[12] These results may not be entirely representative of clinical DA imaging utilization, because of their origin from clinical trials, where selection bias may arise because of pressure to enroll, and/or lowered diagnostic criteria to allow more rapid subject recruitment. It is possible that a relatively higher proportion of subjects receiving versus not receiving DA scans might be “worried well” without structural neurological disorders, and it is also possible, as documented by a PPMI study,[13] that some subjects with SWEDDS later convert to having a DA deficit.

The most common neuropathological findings in those with clinically diagnosed PD who did not have PD at autopsy have been either PSP or MSA. In 3 separate reports, 5 of 8, 11 of 24, and 8 of 10 misdiagnosed cases had either PSP or MSA, in approximately equal numbers.[4–6] In the most recent autopsy-validated study, and the only PD diagnostic accuracy study originating from a formal longitudinal clinicopathological study,[2] 17 of 97 of those with clinically probable PD on first visit (including both short and long disease duration) were not confirmed to be PD neuropathologically. Seven had PSP, 1 had MSA, 5 others had various minor neurodegenerative findings, and 3 had no clear neuropathological findings to explain the parkinsonism. Combining these reports,[2,4–6] 32 of 59 misdiagnosed individuals had either PSP or MSA.

In our center’s experience, by far the single most common cause of misdiagnosed PD is PSP. It is very probable that the majority of PSP cases are never recognized during life, because of absence of the characteristic eye findings.[14–17] Reported incidence rates in the United States, based on clinical ascertainment, generally range from less than 1 per 100,000 to 5 per 100,000 per year, with an age-related increase up to 14.7 per 100,000 per year for those aged 80–99.[18,19] In our longitudinal clinicopathological study, the AZSAND (Arizona Study of Aging and Neurodegenerative Disorders),[20] of 119 elderly subjects that were initially normal to both cognitive and movement disorders assessment, who then went on to death and autopsy after serial annual research assessments, 4 (3.4%) received final clinicopathological diagnoses of PSP, compared to 3 (2.5%) diagnosed as PD.[21] Of 87 subjects that remained normal on their final clinical assessment, 4 had microscopic findings of incidental PSP whereas 17 had microscopic findings of incidental Lewy body disease. Taken together, 8 (6.8%) of the original 119 subjects had pathology consistent with PSP whereas 20 (16.8%) had Lewy body disease. Similar PSP population prevalences have been reported by two Japanese groups. In the first study, 5 of 324 consecutive autopsy cases in a

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geriatric hospital received a clinicopathological diagnosis of PSP and another 8 of 324 were classified as preclinical PSP, together 4% of all autopsies.[22] The second study reported that neuropathological criteria for PSP were met in 29 of 998 serial forensic autopsies, including 4.6% of the cases aged >60.[22] Although these postmortem studies are not unbiased population samples, they nevertheless suggest that PSP is a bigger problem for PD diagnosis than previously assumed, given that the population prevalence and incidence of PSP pathology may be orders of magnitude higher than previously estimated.

The autopsy data reviewed here indicate that, of all subjects clinically diagnosed as early PD, around 40% will not actually have PD.[2–4] The reviewed DA imaging studies suggest that adding DA imaging will likely identify approximately one third of these as SWEDDs, whereas the remaining two thirds, around 25% of the initial presumptive PD group, will likely have a DA deficit attributed to a non-PD condition. These will most often be either PSP or MSA, with corticobasal degeneration a possibility as well.

Efforts must be made to improve diagnostic accuracy in early PD. Incorporation of the International Parkinson and Movement Disorder Society (MDS) diagnostic criteria for PD[24] or MDS research criteria for prodromal PD[25] could potentially improve diagnostic accuracy. The new clinical diagnostic criteria for PD combine supportive clinical findings and exclusionary clinical findings, and clinical red flags, to assist the diagnosis. These criteria have recently been reported[26,27] to improve PD diagnostic accuracy to 94.5%, whereas for PD disease duration <5 years, there are reportedly 95.4% specificity and 68.9% sensitivity using new subcriteria, but only using “expert” clinical diagnosis as the gold standard. A possible impediment to using the MDS research criteria is that they utilize likelihood ratios based on certain genetic, clinical motor and nonmotor, environmental, and imaging factors; many of these have not been validated in an autopsy cohort, and the needed data and/or statistical modeling expertise may not always be available. It has been suggested that the combination of earlier-onset (<55), typical clinical features (focal onset, resting tremor), and focal and asymmetrical posterior putamen dopaminergic depletion makes false-positive diagnosis much lower, but review of DA imaging studies indicates that striatal uptake patterns, though statistically helpful, are not likely to be useful in individual subjects.[28–37]

Unfortunately, there is yet no accurate molecular or clinical in vivo biomarker for synucleinopathies. Cerebrospinal fluid measures of α-synuclein have a large overlap with normal subjects,[38,39] but there is hope for promising methods currently in development, including “seeding” assays for biofluids.[40–43] A PET ligand does not appear to be imminently available.[44] Cardiac imaging with $^{123}$I-MIBG may be able to make the distinction between early PD, PSP, and other parkinsonian disorders,[45] but published studies so far have not included enough early cases. Polygenic risk score has been reported to be correlated with age of PD onset,[46] but neuropathological data will be needed to determine specificity in relation to PSP, MSA, and other causes of parkinsonism.

Smell testing may be useful, given that our own unpublished data found that, in 24 and 71 autopsy-confirmed cases of PSP and PD, respectively, the mean University of Pennsylvania Smell Identification Test (UPSIT) scores for the PD cases were substantially and significantly lower (means/standard deviations [SDs] of 14.7/5.6 vs. 25.1/ 8.0; unpaired,

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two-tailed *t* test, $P < 0.001$). Only 5 of 24 PSP cases (20.8%) had a mean UPSIT score equal to or lower than 20, compared to 58 of 71 (81.7%) PD subjects (chi-square, $P < 0.01$); an UPSIT score of 20 or less was thus around 4 times as likely to indicate a diagnosis of PD. This holds true for subjects whose first smell test was done either before or within 5 years of parkinsonism onset (n = 11 for both PD and PSP; means/SDs 20.6/8.4 and 25.5/6.5, respectively; one-tailed *t* test = 0.07). The early PD cases were more than twice as likely, compared to early PSP cases, to have an UPSIT score less than 25 (8 of 11 vs. 3 of 11; chi-square, $P = 0.033$). The potential importance of smell testing is supported by results from the PPMI study, where the UPSIT score was the most powerful factor in a predictive diagnostic algorithm for early PD.[13]

One area of particular interest is tissue biopsy. Postmortem studies have shown the presence of pathological deposits of α-synuclein in the peripheral nervous system in PD and other Lewy body disorders.[47] Submandibular gland, colon, and skin biopsies have been intensively studied for their potential to improve diagnostic accuracy,[48] and the Michael J. Fox Foundation is currently conducting a multicenter, blinded, clinical study, "S4," that will assess the diagnostic potential of biopsies from all three anatomical sites in 80 subjects.[49] The olfactory bulb could be a very sensitive and specific biopsy target for PD,[50] but to date there have been no clinically based tissue studies.

With many methods in development, autopsy confirmation of new findings will always be the most accurate means with which to assess the utility and validity of new diagnostic tools, and more autopsy-confirmed studies of clinical diagnostic accuracy in early PD are urgently needed. The best clinical surrogate is subjects with longstanding typical PD, supported by DA imaging, where accuracy should be slightly over 90%. Clinical trial planning of early PD should consider incorporating an expected misdiagnosis rate of 25%, even when supported by DA imaging.

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