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SIC Task Force Appraisal of Clinical Diagnostic Criteria for Parkinsonian Disorders

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Abstract: As there are no biological markers for the antemortem diagnosis of degenerative parkinsonian disorders, diagnosis currently relies upon the presence and progression of clinical features and confirmation depends on neuropathology. Clinicopathologic studies have shown significant false-positive and false-negative rates for diagnosing these disorders, and misdiagnosis is especially common during the early stages of these diseases. It is important to establish a set of widely accepted diagnostic criteria for these disorders that may be applied and reproduced in a blinded fashion. This review summarizes the findings of the SIC Task Force for the study of diagnostic criteria for parkinsonian disorders in the areas of Parkinson's disease, dementia with Lewy bodies, progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration. In each of these areas, diagnosis continues to rest on clinical findings and the judicious use of ancillary studies.

Key words: diagnostic criteria; accuracy; reliability; Parkinson disease; progressive supranuclear palsy; corticobasal degeneration; multiple system atrophy; dementia with Lewy bodies

There are no biological markers for the antemortem diagnosis of degenerative parkinsonian disorders, and diagnosis currently relies upon the presence and progression of clinical features. Diagnostic confirmation depends on neuropathology. Clinicopathological studies have shown significant false-positive and false-negative rates for diagnosing these disorders. Misdiagnosis is especially common during the early stages of these diseases, even among movement disorder specialists.[1,2] This limitation strongly affects epidemiologic studies and clinical trials. Ideally, for every disease, there should be a set of widely accepted diagnostic criteria, including one or more well-established reference standard tests, that may be applied and reproduced in a blinded manner.

Because various sets of clinical diagnostic criteria are currently used for the classification of the different progressive degenerative parkinsonian disorders, the Scientific Issues Committee of the Movement Disorder Society formed a Task Force to evaluate current diagnostic criteria. Pairs of members reviewed each disorder (Parkinson's disease, PD; dementia with Lewy bodies, DLB; progressive supranuclear palsy, PSP; multiple system atrophy, MSA; and corticobasal degeneration, CBD) based on a MEDLINE search of the literature up to April 2002 and additional material known to be "in press," and wrote an initial report that was circulated and reviewed by all participants.

Most clinicopathological studies have been retrospective, significantly limiting the conclusions. In general, the number of cases in the published studies have been small, clinical evaluations were not standardized, and diagnostic determinations were performed by different clinicians who were not necessarily trained in movement disorders.[1,3,4] In some studies, it is uncertain if clinical manifestations occurred as early "presenting manifestations," "concurring manifestations" that were present initially but did not prompt patient concern, or "eventual manifestations" that occurred late in the disease. If

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"eventual manifestations" are required for diagnosis, these criteria will never be useful to diagnose early cases.

There are inevitable limitations in the statistical validity measures one uses to review these studies. Thus, the positive and negative predictive values are dependent on the prevalence of a disease in the underlying population. It is likely that there are differences in the disease prevalence in clinical practice vs. the populations enriched with atypical parkinsonism that have been assembled for study and summarized in this review. The higher-than-expected prevalence of atypical parkinsonism in the population studied may overestimate the positive predictive value of the studied diagnostic criteria. Moreover, one should be cautious when comparing positive and negative predictive value results from studies with different underlying disease prevalence. Hence, the sensitivity and specificity may be affected by disease duration, so that these estimates may not perform as well in populations with short disease duration. The current report has been prepared to help clinicians and investigators select the most appropriate set of clinical diagnostic criteria, and to encourage investigators to initiate studies that will address the shortcomings mentioned.

PARKINSON'S DISEASE

Existing Diagnostic Criteria: Validity and Reliability Studies

Several sets of clinical diagnostic criteria for PD have been proposed[3,5–7] (see Table 1 for the most commonly used, but most have not been evaluated for their validity and reliability). Most proposed criteria were based on the authors' experience, but the latest set advanced[5] was based on a literature review. All studies that evaluated the validity of the clinician's judgment as to whether the patient had PD (without established or defined criteria at the start of the study for the diagnosis)[8,9] and those that have tried to define and test the validity of combinations of clinical features required for its diagnosis (Table 2)[3,9] have been retrospective.

The first clinicopathological study[7] found that only 69 to 75% of the patients with the autopsy-confirmed diagnosis of PD had at least two of the three cardinal manifestations of PD: tremor, rigidity, and bradykinesia. Furthermore, 20 to 25% of patients who showed two of these cardinal features had a pathological diagnosis other than PD. Even more concerning, 13 to 19% of patients who demonstrated all three cardinal features typically associated with a clinical diagnosis of PD had another pathological diagnosis.

Rajput and colleagues reported autopsy results in 59 patients with parkinsonian syndromes.[2] All of these patients had been examined longitudinally by a single neurologist who had based the clinical diagnosis of PD on the presence of two of the three cardinal manifestations mentioned above. These authors excluded postural instability as one of the cardinal manifestations, because it is usually not present in early PD. They also used exclusion criteria that included absence of any identifiable cause of

TABLE 1. *UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria*

Inclusion criteria	Exclusion criteria	Supportive criteria
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)	History of repeated strokes with stepwise progression of parkinsonian features	(Three or more required for diagnosis of definite PD)
And at least one of the following:	History of repeated head injury	Unilateral onset
Muscular rigidity	History of definite encephalitis	Rest tremor present
4–6 Hz rest tremor	Oculogyric crises	Progressive disorder
Postural instability not caused by primary visual, vestibular, cerebellar, or proprioceptive dysfunction	Neuroleptic treatment at onset of symptoms	Persistent asymmetry affecting side of onset most
	More than one affected relative	Excellent response (70–100%) to levodopa
	Sustained remission	Severe levodopa-induced chorea
	Strictly unilateral features after 3 yr	Levodopa response for 5 yr or more
	Supranuclear gaze palsy	Clinical course of 10 yr or more
	Cerebellar signs	
	Early severe autonomic involvement	
	Early severe dementia with disturbances of memory, language, and praxis	
	Babinski sign	
	Presence of cerebral tumour or communicating hydrocephalus on CT scan	
	Negative response to large doses of levodopa (if malabsorption excluded)	
	MPTP exposure	

UK, United Kingdom; PD, Parkinson's disease; CT, computed tomography.

TABLE 2. *Accuracy of predictors of Parkinson's disease*

Reference	PD cases/all cases	Diagnostic criteria	Sens.	Spec.	PPV	NPV	Comments and recommendation
Ward and Gibb[7]	24/34	2 of 3 of T, B, R	75	40			Details poor
		3 of 3 of T, B, R	67	14			Details poor
Hughes et al.[8]	76/100	2 of 3 of T, B, R	99	8	77	67	Retrospective
		3 of 3 of T, B, R	65	71	88	40	Retrospective
		Asymmetrical onset and no atypical features	75	75	90	49	Retrospective
		As above & no etiology for another disorder	68	83	93	45	Retrospective
		Marked response to levodopa	79	33	78	35	Retrospective
		Presence of dyskinesia or fluctuations	66	52	83	31	Retrospective
Litvan et al.[9]	15/105	Neurologist judgment	73	86	46	95	Retrospective; mean values of 6 raters analyzing 105 clinical vignettes at first visit
		Primary neurologist dx	93	77	40		Diagnosis made at first visit
		Levodopa-induced dyskinesias; asymmetrical limb rigidity			86	89	Predictors found in logistic regression analysis
		Unilateral tremor at onset; excellent levodopa response			88	87	Using the data collected by 6 raters on the same 105 cases
		Unilateral tremor at onset; levodopa-induced dyskinesias			88	90	
		Rest tremor; no pyramidal signs; excellent levodopa response			88	91	
		Asymmetrical limb rigidity; rest tremor			81	91	
		Asymmetrical limb rigidity; no oculomotor signs; moderate to excellent levodopa response			86	89	

Superscript numbers correspond to the list of References.
Validity values are given as percentages.
T, tremor; B, bradykinesia; R, rigidity; Sens., sensitivity; Spec., specificity; PPV, positive predictive value; NPV, negative predictive value; dx, diagnosis.

parkinsonism or other central nervous system lesions. After a long-term follow-up period, the clinical diagnosis of PD was retained in 41 of 59 patients. However, only 31 of 41 (75%) patients with clinically determined PD showed histopathological signs of PD at autopsy examination.

A third series was composed of 100 patients with a clinical diagnosis of PD, who had been examined during their life by different neurologists using poorly defined diagnostic criteria. When autopsies were performed (mean interval between symptom onset and autopsy 11.9 years),[8] PD was found in 76 patients. The authors reviewed the charts of these patients and then applied the accepted UK Parkinson's Disease Society Brain Bank (UK PDSBB) clinical criteria for PD requiring bradykinesia and at least one other feature, including rigidity; resting tremor; or postural instability and focusing on clinical progression, asymmetry of onset, and levodopa response. Sixteen additional exclusion criteria were also applied (Table 1). With the application of these diagnostic criteria, 89 of the original 100 patients were considered to have PD, but, again, only 73 (82%) were confirmed to have PD at autopsy. When the authors reexamined the patients with all three cardinal features (excluding the postural instability), only 65% of patients with an autopsy diagnosis of PD fit this clinical category.[8] These investigators have since studied the accuracy of the clinical diagnosis of PD in 100 consecutive patients that came to neuropathological examination.[10] Ninety fulfilled pathological criteria for PD. Ten were misdiagnosed: MSA (six), PSP (two), postencephalitic parkinsonism (one), and vascular parkinsonism (one). They next examined the accuracy of diagnosis of parkinsonian disorders in a specialist movement disorders service.[10]

They reviewed the clinical and pathological features of 143 cases of parkinsonism,[11] likely including many of the patients previously reported.[10] They found a surprisingly high positive predictive value (98.6%) of clinical diagnosis of PD among the specialists. In fact, only 1 of 73 patients diagnosed with PD during life was found to have an alternate diagnosis. This study demonstrated that the clinical diagnostic accuracy of PD could be improved by using stringent criteria. Whereas the criteria of UK PDSBB, Calne and coworkers, and Gelb and colleagues were evaluated in this series, the assessment of their validity is limited due the inclusion of only a few non-PD patients.

A particularly large series of 580 patients with clinically determined PD had autopsies performed, and pathological confirmation occurred in 489 (84%).[12] The clinical diagnostic criteria used to arrive at this high diagnostic accuracy were not specified.

Litvan and coworkers reported a study to help formulate criteria to differentiate PD from DLB.[9] Six raters, who were unaware of the neuropathological diagnoses, analyzed 105 clinical vignettes corresponding to 15 cases of PD and 90 patients with other disorders (including DLB). All diagnoses were established through autopsy.[9] Group inter-rater reliability for the diagnosis of PD was moderate at the first visit (median 36 months from symptom onset; $\kappa = 0.54$) and substantial at the last visit ($\kappa = 0.64$). Median sensitivity for the first visit diagnosis of PD was 73.3% and 80.0% at the last visit and median specificity increased from 85.6% to 92.2% from the first to last visit. Among primary neurologists, the sensitivity for the diagnosis of PD at both visits was high (93.3%) but the specificity was lower. At both visits, false-negative diagnoses were uncommon. Closer examination of the PD cases misdiagnosed by at least three raters at the first visit revealed that these were complicated cases. False-positive misdiagnoses were numerous and primarily involved DLB, MSA, and PSP.

The investigators also examined the best predictive diagnostic variables for PD compared to the other diagnoses. Asymmetrical parkinsonism (tremor or rigidity) and levodopa response (moderate to excellent response or levodopa-induced dyskinesias) were the most important discriminative features suggestive of PD. Other significant predictors were rest tremor and the absence of pyramidal or oculomotor signs.

Recent Developments and Future Objectives

Clinicopathological studies are needed to validate the proposed clinical diagnostic criteria for PD. However, these studies are difficult to conduct when there are no universally accepted neuropathological criteria for PD. The identification of three genes, i.e., α-synuclein, Parkin, and ubiquitin C-terminal hydrolase L1, and several additional loci associated with inherited forms of levodopa-responsive PD has confirmed that PD is not a single disorder and has questioned its definition. Lewy bodies, even in sporadic PD, contain these three gene products, with particularly abundant amounts of fibrillar alpha-synuclein. Mutations in the parkin gene, a common cause of PD in patients with very early onset parkinsonism, present with nigral degeneration that it is not accompanied by Lewy-body formation.[13–15] It is debatable whether the inherited forms of levodopa-responsive PD, known to be clinically identical to Lewy body PD, should be included in the neuropathological definition of PD. In some ways, all the accuracy studies reported are flawed, as there are no accepted neuropathological criteria for PD. The lack of accepted neuropathological criteria influences the interpretation of the literature. For example, if we now accept that Parkin is a genetic form of PD, and if the tangle of cases by Rajput and coworkers[2] are Parkin cases, as they may well be, then the diagnostic inaccuracy reported by them was overestimated.

Simultaneously obtained structural and functional neuroimaging may further increase the sensitivity and specificity of these criteria. With the advent of more sophisticated, computer-based measurement techniques, quantification of clinical features like rigidity, tremor, bradykinesia, and dyskinesia may be possible. Standardization of pharmacological response testing is essential to large population-based studies, and repetitive testing will define clinical response thresholds and sustained responses that may be important for diagnostic accuracy. Of course, continued focus on the identification of an accurate biological marker of PD is paramount to the ultimate goal of early disease detection.

DEMENTIA WITH LEWY BODIES

Existing Diagnostic Criteria: Validity and Reliability Studies

Diagnostic criteria for DLB would ideally pass at least two tests. First, the criteria must distinguish DLB from other dementia types, notably Alzheimer's disease (AD) and vascular dementia (VaD), the two most common differential diagnoses in elderly patients with cognitive failure. Second, and more challenging, the criteria must distinguish between DLB and other parkinsonian disorders associated with cognitive and/or psychiatric disorders such as PD later complicated by dementia (PDD) or, less commonly, atypical parkinsonian syndromes, including PSP and CBD. Third, because PD, PDD, and DLB share many clinical and pathological features, it

remains controversial whether they are distinct neurological diseases or different clinical presentations of the same neurological disorder. More importantly, although there are guidelines to evaluate Lewy body pathology,[16] neuropathological criteria for DLB still need to be defined and validated.

To date, five sets of diagnostic criteria have been proposed to assist clinicians in making an accurate diagnosis of DLB (Table 3).[17–21] The criteria have been derived mainly from the extensive clinical experience of the authors. The most rigorous approach led to the formation of the Consensus diagnostic criteria for DLB that were published in 1996.[16] The term DLB was adopted by the DLB Consensus Conference to include all previous appellations, including Lewy body variant of AD,[22] senile dementia of Lewy type,[23] and Lewy body dementia.[24] The focus of the new consensus criteria was to address the objective of distinguishing DLB from other types of dementia. To this end, operationalized criteria[16] were refined by a group of experts with extensive experience in DLB, AD, PD, and PDD to produce mandatory inclusion and exclusion criteria, as well as supportive criteria (Table 4).

TABLE 3. *Published diagnostic criteria for dementia with Lewy bodies*

Reference	Year	Derivation and use
Byrne et al.[24]	1991	Criteria divided into probable and possible, parkinsonism mandatory, PDD included as a subtype of DLB
McKeith et al.[23]	1992	Retrospectively derived from review of 21 pathologically confirmed cases. Fluctuating cognition and 1 of 3 of visual hallucinations, parkinsonism, and repeated falls, or disturbances of consciousness
CERAD criteria Hulette et al.[141]	1995	2 of 3 of delusions or hallucinations, parkinsonism, and unexplained falls or changes in consciousness
Refined 1992 Consensus Criteria McKeith et al.[16]	1996	Require cognitive impairment with attentional and visuospatial deficits and 2 of 3 (probable DLB) 1 of 3 (possible DLB) of fluctuating cognition, visual hallucinations, or parkinsonism
Luis et al.[29]	1999	Empirically derived from review of 35 pathologically confirmed cases; 3 diagnostic categories (A, B, C) requiring 1, 2, or 3 of hallucinations, unspecified parkinsonism, fluctuating course, or rapid progression

Superscript numbers correspond to the list of References.
PDD, Parkinsonism disease and dementia; DLB, dementia with Lewy bodies.

Nine published studies[9,25–32] have reported the diagnostic accuracy of the proposed Consensus diagnostic criteria—these form the basis for the present report. Studies were included (Table 5) if they assessed the diagnostic accuracy of Consensus criteria for possible and/or probable DLB, had pathological confirmation of diagnosis (including multiple cortical LB), and had been published in a journal listed by Medline. All of the selected studies compared DLB to other types of dementia, including AD or VaD. Six of the nine studies were retrospective (i.e., case reports of patients with already established autopsy diagnoses) and were usually reviewed by several independent assessors of varying experience. Only two studies[27,30] with subsequent postmortem examination, categorized diagnoses during the patient's lifetime using agreement of experienced clinicians as the entry criterion.

A total of 135 pathologically confirmed DLB cases have been compared with 350 non-DLB cases. Considering all studies together, the sensitivity of a diagnosis of probable DLB varies from 0 to 83% (mean, 49%), specificity 79 to 100% (92%), positive predictive value (PPV) 48 to 100% (77%), and negative predictive value 43 to 100% (NPV) (80%). The study by Lopez and colleagues[28] is notable in that none of the four clinical raters ever diagnosed probable DLB in a sample of 40 dementia cases, 8 of whom had autopsy-confirmed LB pathology. This result is clearly at odds with the other reports, and the zero value for sensitivity substantially reduces the overall mean value. The first study to have prospectively applied Consensus criteria and then followed patients to autopsy, reports the highest levels of diagnostic accuracy to date.[30] False-negative diagnoses of DLB were associated with additional comorbidity, particularly evidence of cerebrovascular disease from the clinical history, examination, or neuroimaging. In contrast, a more recent prospective study performed at a dedicated AD research center, reported that only 23% of cases with cortical Lewy body pathology had a antemortem diagnosis of probable DLB.[27] This low sensitivity, in part, may be because a high proportion (50%) of all demented cases reaching autopsy had "cortical LB" in structures, including amygdala, which may accumulate LB in late stage AD, but which were not specified in the pathological consensus criteria for DLB. There is general agreement, however, that DLB is harder to recognize clinically as the burden of Alzheimer pathology increases.

Sensitivity of a diagnosis of possible DLB is greater than that of probable DLB; however, there is also considerable loss of specificity as shown by Verghese and

TABLE 4. *Consensus criteria for the clinical diagnosis of probable and possible dementia with Lewy bodies (16)*

Diagnostic categories	Inclusion criteria	Exclusion criteria	Supportive criteria
Possible	Progressive cognitive decline of sufficient magnitude to interfere with normal social or occupational function. Prominent or persistent memory impairment may not necessarily occur in the early stages but is usually evident with progression. Deficits on tests of attention and of frontal-subcortical skills and visuospatial ability may be especially prominent One of three core features: (a) Fluctuating cognition with pronounced variations in attention and alertness (b) Recurrent visual hallucinations (c) parkinsonism	For possible and probable: Stroke disease or evidence of any other brain disorder sufficient to account for the clinical picture	Repeated falls, syncope, transient loss of consciousness, neuroleptic sensitivity, systematized delusions, hallucinations in other modalities[a]
Probable	Possible criteria plus one core feature		
Definite	Autopsy confirmation		

[a]Depression and rapid eye movement sleep behavior disorder have since been suggested as additional supportive features.[35]

TABLE 5. *Validity and reliability of consensus criteria for dementia with Lewy bodies*

Reference	DLB cases/all cases	Diag. criteria	Sens.	Spec.	PPV	NPV	κ	Comments and recommendations
Mega et al.[31]	4 DLB/24 AD	Prob.	75	79	100	93	F = 0.25 H = 0.59	Retrospective; suggest 4 of 6 of H, C, R, B, N, Fl
		Poss.	NA	NA	NA	NA	P = 0.46	
Litvan et al.[9]	14 DLB/105 PD, PSP, MSA, CBD, AD	[a]	18	99	75	89	0.19–0.38	Retrospective; no formal criteria for DLB used; comparison mainly with movement disorder patients
Holmes et al.[26]	9 DLB/80 AD, VaD	Prob.	22	1.00	100	91	NA	Retrospective; no specific recs.; mixed pathology cases hardest to diagnose
		Poss	NA	NA	NA	NA		
Luis et al.[29]	35 DLB/56 AD	Prob.	57	90	91	56	F = 0.30 H = 0.91	Retrospective; suggest H, P, Fl, and rapid progression
		NA	NA	NA	NA	NA	P = 0.61	
Verghese et al.[32]	18 DLB/94 AD	Prob.	61	84	48	90	F = 0.57 H = 0.87	Retrospective; suggest 3 of 6 of P, Fl, H, N, D and F
		Poss.	89	28	23	91	P = 0.90	
Lopez et al.[28]	8/40		0	100	0	80		Retrospective; probable DLB not diagnosed once by team of 4 raters; no specific recs.
Hohl et al.[25]	5 DLB/10 AD	Prob.	100	8	83	100	NA	Consensus criteria applied retrospectively; clinician diagnosis without Consensus criteria had PPV of 50
		Poss.	100	0	NA	NA		
McKeith et al.[30]	29 DLB/50 AD, VaD	Prob.	83	95	96	80	NA	Prospective; false negatives associated with comorbid pathology
		Poss.	NA	NA	NA	NA		
Lopez et al.[27]	13 DLB/26 AD	Prob.	23	100	100	43		Prospective, met NINCDS-ADRDA criteria for AD, only 4 of them met DLB criteria
		Poss.	NA	NA	NA	NA		

Validity values are given in percentages. Superscript numbers correspond to the list of References.

[a]No criteria applied, retrospective clinical diagnosis.

DLB, dementia with Lewy bodies; AD, Alzheimer disease; PD, Parkinson's disease; PSP, progressive supranuclear palsy; MSA, multiple system atrophy; CBD, corticobasal degeneration; VaD, vascular dementia; Sens., sensitivity; Spec., specificity; PPV, positive predictive value; NPV, negative predictive value; κ, kappa statistic (inter-rater reliability); Prob., probable; Poss., possible; H, hallucinations; C, cogwheeling, R, rigidity; B, bradykinesia; N, neuroleptic sensitivity; Fl, fluctuation; D, delusions; F; falls; P, parkinsonism; NA, not available.

coworkers,[32] who reported a sensitivity of 89% and a specificity of 28% in a total of 94 dementia cases with postmortem diagnosis verified by autopsy. The remaining studies did not systematically explore the validity of the consensus criteria for possible DLB.[25,30,31]

Inter-rater reliability for a diagnosis of probable DLB has been reported by only one study[24] with $\kappa = 0.80$, indicating excellent agreement. However, the number of cases examined was only 10. Litvan and colleagues[9] found $\kappa = 0.38$ (early stage illness) through 0.19 (late stage), in a series of cases where the diagnosis of DLB was based on clinical judgment without using specific diagnostic criteria. Kappa values for individual DLB core symptoms have also been reported. For parkinsonism (0.46–0.90) and hallucinations (0.59–0.91), inter-rater agreement is generally good; but for fluctuation, it is less reliable (0.25–0.57). The Second International Workshop identified the development of operationalized criteria for defining cognitive fluctuation as a research priority. Walker and coworkers[34] recently have published three standardized methods for quantifying fluctuation, methods that hold potential to significantly increase reliability and validity of diagnosis. The Clinician Assessment of Fluctuation is a clinician-administered severity scale, the One Day Fluctuation Assessment Scale is based on a caregiver questionnaire, and the third method measures the coefficient of variance of response times on a repeatedly administered, computerized choice reaction task.[35]

Taken together, these data support the conclusion of the Second International Workshop on DLB that the Consensus criteria for probable DLB are appropriate for confirmation of diagnosis (few false positives) when attempting to diagnose DLB in a demented population but may be of limited value in screening for DLB cases (high false negative rate). Clinical underdiagnosis of DLB remains a problem in all but a few highly specialized centers, AD being the most frequent misdiagnosis of autopsy-confirmed DLB cases.[27,36] The diagnosis of DLB in a parkinsonian population remains a challenge.

Recent Developments and Future Objectives

Although there is an emerging consensus about diagnostic criteria capable of identifying DLB cases with high specificity (probable DLB) among subjects with dementia, there has been little systematic research into ways of increasing diagnostic sensitivity. Previous recommended criteria for "possible" DLB have been composed of shortened lists of core symptoms. This method achieves a modest increase in sensitivity of case detection at the expense of markedly reduced specificity. Although this approach is a reasonable preliminary strategy, more work needs to be done to describe the wider range of clinical presentations associated with DLB. Criteria for DLB also need to acknowledge the frequent occurrence of cases with mixed pathology cases (predominantly vascular and AD).

With regard to the relationship between DLB and PD, it is now clear that DLB does not always represent a spread of Lewy bodies and neuronal loss from subcortical to cortical structures. This finding may occur in some PD cases that develop neuropsychiatric features and cognitive impairment late in their illness. However, in DLB cases presenting de novo, paralimbic and neocortical LB densities are highly correlated with each other but not with the extent of nigral pathologic state. Such patients are likely to be older than those with PD and have significantly shorter survival rates. This finding suggests that DLB should not just be considered a severe form of PD[36] but that PD and DLB are different expressions of a shared underlying pathological process or even extreme phenotypes of the same disorder. Future modifications of diagnostic criteria, and the associated validation studies, would ideally include the full range of clinical presentations that can be associated with LB disease (movement disorder, cognitive failure, autonomic dysfunction, psychiatric symptoms, and/or sleep disorder). However, such a broad classification would probably be of limited acceptability and application in clinical practice. Recognition that a series of typical clinical phenotypes may overlap with one another (PD, DLB, and autonomic failure) and may change with time will probably be the most productive basis upon which to develop more accurate and clinically useful diagnostic algorithms.

PROGRESSIVE SUPRANUCLEAR PALSY

Existing Diagnostic Criteria: Validity and Reliability Studies

Seven different sets of diagnostic criteria have been proposed for PSP (Table 6).[1,37–42] In the majority, the criteria were not derived in a systematic manner but were compiled mainly from the extensive clinical experience of the authors and there is a considerable overlap among them. A progressive condition, with onset over the age of 40 or 45, and supranuclear gaze palsy are common to all the existing criteria. With the exception of the diagnostic criteria proposed by Lees and Blin and colleagues, all the other sets include explicit mandatory exclusion criteria.[37,40] Three sets of criteria specifically state either "nonfamilial disorder" or "no family history."[40–42] Whether a recent report of 12 families with clustering of PSP calls into question this stipulation needs to be investigated.[43]

TABLE 6. *Published diagnostic criteria for PSP*

Reference	Year	Derivation and use
Lees[40]	1987	Defined as progressive non-familial disorder beginning in middle or old age with SNO and = two of five "cardinal features"[a]
Blin et al.[37]	1990	Defined as "probable" if all of nine criteria are met or "possible" if seven of nine are fulfilled[a]
Duvoisin[38]	1992	Criteria divided into four sections—essential for diagnosis, confirmatory manifestations, manifestations consistent with but not diagnostic of PSP and features inconsistent with PSP[a]
Golbe[39]	1993	Defined as onset after age 40, progressive course bradykinesia and SNO, plus three of six further features, plus absence of three "inconsistent" clinical features[a]
Tolosa et al.[41]	1994	Defined as a non-familial disorder of onset after age 40, progressive course and SNO, plus = three of five further features for "probable" and two of five for "possible", plus absence of five "inconsistent" clinical features[a]
Collins et al.[42]	1995	Retrospectively from review of 12 pathologically confirmed cases; algorithm based, including prerequisites & exclusionary criteria; SNO and/or prominent postural instability, plus a number of other specified signs
Litvan et al.[1]	1996	Systematic literature review, logistic regression & CART analysis; validated using data from postmortem confirmed cases; "definite", "probable", & "possible" categories described (see Table 7, text)

Features among different set of criteria overlap. Superscript numbers correspond to the list of References. See articles for more details.

[a]Based on the experience of the investigator.

SNO, supranuclear ophthalmoparesis; CART, classification and regression tree analysis.

Because bradykinesia affects nearly half of the patients by the time of diagnosis and up to 95% of patients during the course of their illness[44,45] and a frontal lobe-like syndrome also develops in the majority of cases (80% of cases in total, 52% in the first year),[45–48] ideal diagnostic criteria for PSP would reliably separate this condition from other neurodegenerative disorders with parkinsonism and dementia,[49] particularly with a fronto-subcortical pattern of involvement.[28]

The most rigorous approach to date led to the formulation of the National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy, Inc. (NINDS-SPSP) diagnostic criteria (Table 7).[50] Initially, new preliminary criteria were proposed and validated following a systematic review of the literature and critique of existing diagnostic criteria. The validation process used a data set of clinical information, derived retrospectively from the records of patients with pathologically confirmed PSP and other disorders presenting with dementia and parkinsonism. Neurologists with a special interest in movement disorders and blinded to the pathological diagnoses were then asked to assign a diagnosis to each case on the basis of the clinical vignettes provided. Finally, the criteria were refined by a group of experts with extensive experience in PSP to produce mandatory inclusion and exclusion criteria, as well as supportive criteria.

The sensitivity, specificity, and positive predictive value of the NINDS-SPSP criteria have been evaluated retrospectively in a pathologically confirmed series of 83 patients. From this analysis, the NINDS-SPSP criteria appear to have superior specificity, sensitivity, and positive predictive value when compared to other PSP diagnostic criteria (Table 8). The accuracy of the NINDS-SPSP clinical diagnostic criteria have also been evaluated along with existing criteria for three other dementing disorders by a different group of raters in an independent sample of pathologically confirmed cases.[28] This study confirmed that both the probable and possible NINDS-SPSP criteria for PSP had excellent specificity (Table 8). Postural instability leading to falls within the first year of disease onset, coupled with a vertical supranuclear gaze paresis have good discriminatory diagnostic value when comparing PSP with other disorders with parkinsonism and dementia.[28,51]

Hughes and coworkers recently have reported the accuracy of diagnosis of PSP and other parkinsonian syndromes in a specialist movement disorder service.[11] There were 19 pathologically confirmed cases of PSP in their series of 143 cases of parkinsonism. Positive predictive value, sensitivity, and specificity for diagnosis of PSP were 80.0%, 84.2%, and 96.8%, respectively. Specific diagnostic criteria were not applied for the diagnosis of PSP in this study, reflecting, perhaps, the use of some innate form of pattern recognition by movement disorder specialists. This situation is clearly not applicable to all physicians likely to be seeing PSP patients. It is noteworthy that almost two-thirds of the cases in this series with a final clinical diagnosis of a parkinsonian syndrome other than PD had their diagnosis changed. The disease duration at the time of final clinical diagnosis, therefore, was significantly longer in the PSP patients than it was in the PD patients. Although experts in movement disorders, therefore, may have a high degree of accuracy for diagnosis of PSP, early diagnosis is still problematic.

Clinicopathological series, from which much of the above data has been derived, may be biased toward

TABLE 7. *NINDS-SPSP clinical criteria for the diagnosis of PSP*

Diagnostic categories	Inclusion criteria	Exclusion criteria	Supportive criteria
	For possible and probable: Gradually progressive disorder with age at onset at 40 or later;	*For possible and probable:* Recent history of encephalitis; alien limb syndrome; cortical sensory deficits; focal frontal or temporoparietal atrophy; hallucinations or delusions unrelated to dopaminergic therapy; cortical dementia of Alzheimer type; prominent, early cerebellar symptoms or unexplained dysautonomia; or evidence of other diseases that could explain the clinical features	Symmetric akinesia or rigidity, proximal more than distal; abnormal neck posture, especially retrocollis; poor or absent response of parkinsonism to levodopa; early dysphagia & dysarthria; early onset of cognitive impairment including $>$ 2 of: apathy, impairment in abstract thought, decreased verbal fluency, utilization or imitation behavior, or frontal release signs
Possible	Either vertical supranuclear palsy or both slowing of vertical saccades & postural instability with falls $<$ 1 yr disease onset		
Probable	Vertical supranuclear palsy and prominent postural instability with falls within first year of disease onset[a]		
Definite	All criteria for possible or probable PSP are met and histopathologic confirmation at autopsy		

Adapted from Litvan et al., 1996.[50]

[a]Later defined as falls or the tendency to fall (patients are able to stabilize themselves).

NINDS-SPSP, National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy, Inc.; PSP, progressive supranuclear palsy.

atypical cases[42,52] as such patients are more likely to be referred through specialist movement disorder clinics and may not be representative of community-based PSP cases. In the UK, 65% of PSP patients present to a specialist other than a neurologist and 13% never see a neurologist.[53]

The development of "core" diagnostic features of PSP may be delayed, or may not occur at all. In one series, comprising 17 pathologically confirmed cases of PSP, 10 of the cases did not have a vertical supranuclear gaze paresis documented antemortem. Furthermore, these PSP patients "*sine* supranuclear gaze paresis" were reported to have a longer disease duration, fewer falls, and less bulbar dysfunction than patients with ophthalmoparesis.[54] Even though each patient in this series had seen a neurologist at some stage of their illness, all 10 patients without a supranuclear gaze paresis were misdiagnosed.

Pathologically confirmed cases of PSP have been reported in which there was pure akinesia, whereas others have documented early and severe dementia.[55,56] Additional reports have described features that would conventionally be considered to be unusual for PSP, including unilateral limb dystonia or apraxia, prominent tremor, and cricopharyngeal dysfunction.[57–61]

PSP is most often clinically misdiagnosed as PD or VaD (false-negative clinical diagnosis).[1,49,53] In one clinicopathological series, 25% of 24 cases clinically diagnosed as having PD (but without LB during postmortem) were found to have PSP.[8] Conversely, there are pathologically confirmed cases of CBD, MSA, DLB, subcortical gliosis, prion disease, and Whipple's disease, that were clinically misdiagnosed as having PSP (false-positive clinical diagnosis).[1,62–64]

Recent Developments and Future Objectives

The average patient with PSP remains undiagnosed for approximately 3 years, approximately half of the natural history of their disease.[44,65] It is at this time when the patients are likely to be seen by specialists other than neurologists, and they are most likely to be misdiagnosed.[2] Consequently, how the NINDS-SPSP criteria, or any other diagnostic criteria proposed, perform in the first few years of the illness is unknown. Prospective, community based clinicopathological studies of early parkinsonism or "indeterminate" akinetic-rigid syndromes are clearly needed to address this issue.[66]

Because the specificity and PPV of the probable NINDS-SPSP clinical criteria have been found to be near perfect, and the specificity and PPV of the possible criteria to be high (Table 7), a redefinition of this set of criteria has been proposed.[67] This renames as *clinically definite* the previous probable NINDS-SPSP criteria and

TABLE 8. *Validity and reliability of diagnostic criteria for PSP*

Reference	PSP cases/all cases	Diagnostic criteria	Sens.	Spec.	PPV	NPV	κ	Comments and recommendations
Litvan et al.[1]	24/105	Lees[40]	53	95	77	88	0.81	Diagnosis of 6 neurologists using these criteria when evaluating clinical vignettes (values reported are from the first clinical evaluation)
		Blin et al.[37] Probable	13	100	100	80	0.71	
		Blin et al.[37] Possible	55	94	73	87	0.78	
		Golbe[39]	49	97	85	87	0.74	
Litvan et al.[142]	24/83	Lees[40]	58	95	82			Features extracted from 83 cases with detailed clinical information
		Blin et al.[37] Probable	21	100	100			
		Blin et al.[37] Possible	63	85	63			
		Golbe[39]	50	98	92			
		Tolosa et al.[41] Possible	54	98	93			
		Tolosa et al.[41]	54	98	93			
		Collins Verified	25	100	100			
		Collins et al.[42] Possible	42	92	67			
		NINDS-SPSP Probable	50	100	100			
		NINDS-SPSP Possible	83	93	83			
Lopez et al.[28]	8/40	NINDS-SPSP Probable	62	100	100	92	0.72 thru 0.91	Diagnosis of 4 physicians reviewing the first clinical evaluation of patients with dementia and/or parkinsonism
		NINDS-SPSP Possible	75	99	96	95		

Three published studies have reported the diagnostic accuracy of the PSP. Two of the studies used overlapping cases but different methodology (Litvan et al., 1996[1]; Litvan et al., 1997[142]). Validity values are given in percentages.

Sens., sensitivity; Spec., specificity; PPV, positive predictive value; NPV, negative predictive value; κ, kappa statistic (inter-rater reliability); NINDS-SPSP, National Institute of Neurological Disorders and Stroke and Society for Progressive Supranuclear Palsy, Inc.; PSP, progressive supranuclear palsy.

as *clinically probable* the previous possible NINDS-SPSP criteria. The high specificity of these criteria is important for clinical research studies, but their sensitivity is suboptimal for clinical care and descriptive epidemiological studies (Table 7). In an attempt to improve the sensitivity of clinical diagnosis, a new set of possible criteria to include patients with early PSP, thus, is proposed. Patients will be considered as *clinically possible* PSP if they suffer from a gradually progressive disorder of more than 12 months duration, with onset over 40 years of age, and with a tendency to fall within the first year of disease onset, in the absence of defined exclusion criteria (Table 7). There should be no clinical features suggestive of Creutzfeldt-Jakob disease or any other identifiable cause for their postural instability.

In the face of an increasing range of phenotypic variation, it seems inevitable that even the most rigorous clinical diagnostic criteria will have suboptimal sensitivity and specificity. Future studies, therefore, will need to determine whether ancillary investigations can improve diagnostic accuracy, both individually and in combination.[66] Such investigations should include 1) neuro-psychometric testing (including cognitive and behavioral assessments), 2) structural (including magnetic resonance spectroscopy[68]) and functional imaging, 3) neurophysiological studies (including startle responses, eye blink conditioning, sleep), and 4) neuro-ophthalmological studies.

The similarities between PSP and CBD led researchers to question if these are two different nosologic disorders or two extreme phenotypes of the same disorder. However, despite that PSP and CBD share very similar, if not identical, neurochemical and genetic defects,[69–71] their clinical and pathological features are usually quite different (see Dickson et al., 2003[143]) and are considered different entities at present.

MULTIPLE SYSTEM ATROPHY

Existing Diagnostic Criteria: Validity and Reliability Studies

MSA is characterized, clinically, by the combination of varying degrees of parkinsonism, autonomic dysfunction, and impaired cerebellar function; and, pathologically, by the presence of glial cytoplasmic inclusions (GCIs, Papp-Lantos bodies) in oligodendrocytes.[72] The current nomenclature is MSA-P, in which parkinsonism is more prominent, and MSA-C, in which cerebellar dysfunction is more prominent. In 1989, Quinn proposed the first criteria for diagnosing MSA-P (possible, probable, and definite) and MSA-C[73] (probable and definite categories only). At that time, the terms striatonigral degeneration for the predominant parkinsonian picture and sporadic olivopontocerebellar atrophy (sOPCA) for the predominantly cerebellar syndrome were used. These criteria were subsequently modified in 1994 (Table 9)[74] as follows: a category of possible MSA-C composed of a sporadic adult-onset cerebellar syndrome with parkinsonism was introduced, probably unwisely, because it did not specify that the cerebellar syndrome should predominate, and, therefore, most such cases would also qualify for probable MSA-P; a pathological sphincter electromyogram was added as an alternative finding pointing to probable MSA; autonomic failure or pathological sphincter electromyogram (EMG) became obligatory for probable MSA-C but not for MSA-P; the definition of sporadic came about when there was no other case of MSA among first- or second-degree relatives; to allow a diagnosis of probable MSA-P in levodopa-responsive cases a moderate or good, but often waning, response to levodopa was acceptable, provided that *multiple* atypical features were also present.

In 1998, a group of experts convened in Minneapolis, Minnesota, to develop a consensus statement on the diagnosis of MSA (Tables 10 and 11).[75] These criteria essentially operationalized the previous Quinn criteria. The only major difference was that, first, whereas one could diagnose probable MSA in the absence of clear autonomic failure under the Quinn criteria, this is not the case under the consensus criteria, which insist on the presence of autonomic failure for a probable diagnosis. Second, that no ancillary investigations were included.

A different approach was taken by Colosimo and colleagues[76] and later by Wenning and coworkers.[4] Colosimo and colleagues attempted to identify factors that could assist in the early differentiation of MSA-P from PD and PSP. Among 27 cases of pathologically confirmed MSA collected consecutively by the UK PDSBB, 16 cases that presented with only parkinsonian signs during the first 3 years after disease onset were selected. Five clinical parameters, present during the first 3 years after symptom onset that were considered to possibly differentiate MSA-P from PD and PSP, were chosen. The frequencies of these features in MSA were compared to 20 consecutive pathologically confirmed cases of PD and 16 consecutive cases of pathologically confirmed PSP from the same brain bank. The five parameters were: 1) rapid progression of disease (i.e., to Hoehn and Yahr stage 3), 2) symmetrical onset, 3) absence of rest tremor, 4) poor or no response to levodopa (i.e., improvement less than 30% with an intake of L-dopa not lower than 800 mg/day), and 5) cardiovascular autonomic testing showing moderate to severe autonomic involvement (according to Ewing's criteria).[77] For these five features, a comparison of the MSA cases to the PD and PSP cases revealed 1) rapid progression (68.7/10/93.8%; MSA/PD/PSP), 2) symmetric onset (43.7/25/81.3%), 3) absence of rest tremor (87.5/40/62.5%), 4) no or poor benefit to levodopa (31.2/0/75%), and 5) orthostatic hypotension (68.7/5/0%). When assigning one

TABLE 9. *Quinn criteria for Multiple System Atrophy*[73]

Diagnostic categories	MSA-P*	MSA-C*
Possible	Sporadic adult-onset (≥ 30 yr) non/poorly levodopa responsive parkinsonism	Sporadic adult-onset (≥ 30 yr) cerebellar syndrome with parkinsonism
Probable	Possible criteria plus severe symptomatic autonomic failure,[a] and/or cerebellar or pyramidal signs; or pathological sphincter EMG	Sporadic adult-onset cerebellar syndrome, with or without parkinsonism or pyramidal signs, plus severe symptomatic autonomic failure[a] or pathological sphincter EMG
Definite	Postmortem confirmed	Postmortem confirmed

*Without dementia, generalized tendon areflexia, prominent downgaze supranuclear palsy, or other identifiable cause.

[a]Defined as postural syncope and/or marked urinary incontinence or retention not due to other causes.

EMG, electromyogram.

TABLE 10. *Consensus criteria for the diagnosis of MSA*

Clinical domain	Features	Criteria
Autonomic and urinary dysfunction	Orthostatic hypotension (by 20 mm Hg systolic or 10 mm Hg diastolic); urinary incontinence or incomplete bladder emptying[a]	Orthostatic fall in blood pressure (by 30 mm Hg systolic or 15 mm Hg diastolic) and/or urinary incontinence (persistent, involuntary partial or total bladder emptying, accompanied by erectile dysfunction in men)[a]
Parkinsonism	B, R, I, and T	1 of 3 (R, I, and T) and B
Cerebellar dysfunction	Gait ataxia; ataxic dysarthria; limb ataxia; sustained gaze-evoked nystagmus	Gait ataxia plus at least one other feature
Corticospinal tract dysfunction	Extensor plantar responses with hyperreflexia	No corticospinal tract features are used in defining the diagnosis of MSA[b]

[a]Note the different figures for orthostatic hypotension depending on whether it is used as a feature or a criterion.

[b]In retrospect, this criterion is ambiguously worded. One possible interpretation is that, while corticospinal tract dysfunction can be used as a *feature* (characteristic of the disease), it cannot be used as a *criterion* (defining feature or composite of features required for diagnosis) in defining the diagnosis of MSA. The other interpretation is that corticospinal tract dysfunction cannot be used at all in consensus diagnostic criteria, in which case there is no point mentioning it.

MSA, multiple system atrophy; B, bradykinesia; R, rigidity; I, postural instability; T, tremor.

point to each of these factors, the mean for the MSA group (2.9 ± 0.8; mean ± SD) differed significantly from that of the PD cases (0.8 ± 1.0) but not from that of the PSP cases (3.1 ± 1.2). Although MSA and PSP appeared similar in these characteristics, the early appearance of vertical gaze palsy (50%) and axial dystonia (56.2%) allowed relatively easy differentiation of the two disorders.

Wenning and coworkers[4] reviewed the clinical records of 100 autopsy-proven cases of PD and 38 autopsy-proven cases of MSA (Table 12), again from the UK PDSBB, and performed multivariate logistic regression analysis to choose and assign weight to key variables for the optimum predictive model. The following items were identified and given weight (reported in brackets): poor (less than 50% subjective or objective) initial response to levodopa [2], presence of one or more features of autonomic failure [2], speech or bulbar problems present [3], absence of dementia [2], absence of toxic confusion [4], and presence of falls [4]. The maximum score was 17, with the best compromise score being 11 of 17. This finding resulted in a sensitivity of 90.3% and specificity of 92.6%.

Wenning and coworkers[4] then developed a model based on the emergence of features within the first 5 years of the illness. The four significant predictors that emerged were presence of autonomic features [2], poor initial response to levodopa [2], early fluctuations within the first 5 years [2], and initial rigidity as a presenting feature [2]. The last two of these predictors had not been featured in the first model. A cutoff score of ≥ 4 resulted in a sensitivity of 87.1% and a specificity of 70.5%. Of note, 23% of the PD subjects' initial response to levodopa was poor, whereas 58% of MSA cases had a poor

TABLE 11. *Consensus diagnostic categories and exclusion criteria for MSA*

Diagnostic categories	Inclusion criteria	Exclusion criteria
Possible	One criterion plus two features from separate other domains. When the criterion is parkinsonism, a poor levodopa response qualifies as one feature (hence, only one additional feature is required)	*For possible and probable:* Symptomatic onset < 30 yr of age; Family history of a similar disorder; Systemic diseases or other identifiable causes for features listed in Table 10;
Probable	One criterion for autonomic failure/urinary dysfunction plus poorly levodopa responsive parkinsonism or cerebellar dysfunction	Hallucinations unrelated to medication; DSM criteria for dementia; Prominent slowing of vertical saccades or vertical supranuclear gaze palsy;
Definite	Pathologically confirmed by the presence of a high density of glial cytoplasmic inclusions in association with a combination of degenerative changes in the nigrostriatal and olivopontocerebellar pathways	Evidence of focal cortical dysfunction such as aphasia, alien limb syndrome, and parietal dysfunction; Metabolic, molecular genetic, and imaging evidence of an alternative cause of features listed in Table 10

MSA, multiple system atrophy; DSM, *Diagnostic and Statistical Manual for Mental Disorders.*

TABLE 12. *Validity and reliability of diagnostic criteria for MSA*

Reference	MSA cases/all cases	Diagnostic criteria	Sens.	Spec.	PPV	Comments and recommendations
Litvan et al., 1998[78]	16/105	Quinn (1994) possible[a]	53	79	30	Much lower PPV than in Osaki et al. study (below), but different method and case-mix
At first visit (median 3.5 yr)	16/105	Quinn (1994) probable[a]	44	97	68	
Wenning et al., 2000[4];						
Within first 5 yr	38/138	≥ 4 of 8 items present	87	70		
At death (MSA mean duration 6.8 yr, IPD 13.2 yr-duration at last visit not separately specified)	38/138	≥ 11 of 17 items present	90	93		Validity assessed in same sample from which criteria were derived (no cross-validation analysis)
Osaki et al., 2003[79]; At first visit (duration not specified)	51/59	Clinician's prospective diagnosis in life	22		92	Best sensitivity (63%) but lowest PPV (82%) for Quinn possible
		Quinn (1994) possible[a]	63		82	
		Gilman et al. (1999) possible[a]	28		93	
			37		95	
		Quinn (1994) probable[a]	16		100	
		Gilman et al. (1999) probable[a]				
At last visit (mean duration at death 7.5 yr for "true" MSA, and 10.4 yr for false-positive cases, duration at last visit not specified		Clinician's prospective diagnosis in life	100		86	Similar sensitivity and PPV for all except for low sensitivity (63%) for Gilman et al. probable
		Quinn (1994) possible[a]	98		86	
		Gilman et al. (1999) possible[a]	92		86	
		Quinn (1994) probable[a]	94		87	
		Gilman et al. (1999) probable[a]	63		91	
Hughes et al., 2002[11]	34/143	Queen Square Movement Disorder neurologists' prospective diagnosis	88		86	Prospective diagnosis in life

Values given as percentages. Superscript numbers correspond to the list of References.
[a]Atypical retrospectively.
Sens, sensitivity; Spec., specificity; PPV, positive predictive value; MSA, multiple system atrophy; IPD, idiopathic Parkinson's disease.

response. Autonomic failure occurred in 84% of the MSA cases but also in 26% of the PD cases. Dementia and psychiatric symptoms were more common in PD than MSA, and speech impairment and axial instability were almost universal in the MSA cases.

Litvan and colleagues[78] retrospectively applied the 1994 Quinn criteria (Table 12)[73] to data collected by six neurologists while evaluating 105 abstracted clinical vignettes from neuropathologically confirmed cases (16 with MSA, the other 89 bearing 10 other diagnoses). Of interest, no patient had undergone a sphincter EMG and, even at last visit, 55% had never been exposed to levodopa. As would be expected, at first visit (median symptom duration 42 months) the validity of criteria for possible MSA was poor (sensitivity 53% [50–69%]; specificity 79% [69–84%]; and PPV 30% [28–39%]). For probable MSA, specificity improved at the expense of sensitivity (sensitivity 44% [31–60%]; specificity 97% [93–98%]; and PPV 68% [54–80%]).

Osaki and coworkers[79] adopted a different approach, analyzing 59 cases in the Queen Square Brain Bank for Neurological Disorders (formerly the UK PDSBB) with a clinical diagnosis of MSA in life. At autopsy, 51 had MSA, 6 Lewy body disease, and 1 each PSP and cerebrovascular disease. Quinn[74] and Gilman and colleagues[75] diagnostic criteria were retrospectively applied and compared to the clinician's prospective diagnosis at first and last visits. At first visit, the possible criteria of Quinn had the greatest sensitivity (63%) but only 82% PPV, whereas the possible criteria of Gilman and colleagues had the lowest sensitivity (16%) but 100% PPV. At last visit, all criteria other than the probable of Gilman

and colleagues (63%) had ≥ 92% sensitivity and similar PPVs (86–91%).

Hughes and coworkers[11] reviewing material from the same brain bank, specifically studied 143 cases of parkinsonism seen by neurologist associated with the movement disorders service at the National Hospital for Neurology and Neurosurgery, Queen Square, between 1990 and 1999. They found the sensitivity of a clinical diagnosis of MSA made by these specialists to be 88% (30 of 34) and the PPV to be 86% (30 of 35).

One problem with rigid and limited "core" clinical diagnostic criteria is that they can be too restrictive. Faced with a patient with MSA, the history and clinical examination provides information beyond the simple combination of parkinsonism, cerebellar and pyramidal features, and autonomic failure, as defined in the various criteria. Thus, patients may also exhibit a constellation of other "softer" features, including REM sleep behavior disorder, cold discolored extremities, inspiratory sighs, snoring, stridor, myoclonus, emotional incontinence, croaking, quivering, severely hypophonic speech, disproportionate antecollis, contractures, the "Pisa syndrome," early postural instability or falls, and absence of marked cognitive deficits. Even when patients do not display sufficient core criteria to meet existing diagnostic sets, the presence of a combination of these features can be highly suggestive of MSA and may need to be incorporated in future clinical diagnostic criteria.

Recent Developments and Future Objectives

None of the existing sets of diagnostic criteria have been validated in a prospective study with postmortem verification. The European and North American MSA Study Groups (EMSA-SG, NAMSA-SG) have begun a project to develop further consensus on diagnostic criteria and to ultimately test these criteria with postmortem examination. Clearly better diagnostic criteria during the early stages of the disease are needed. This problem will become more urgent once drugs are developed to slow the progression of MSA and treat it symptomatically.

CORTICOBASAL DEGENERATION

Existing Diagnostic Criteria: Diagnostic Accuracy

There are diagnostic criteria for CBD, but none of them have been validated formally (Tables 13–15).[80–87] Most are based on the clinical experience of the authors alone or combined with cases described in the literature and are without pathological confirmation. Also, all of them define a movement disorder, which may pose a selection bias toward motor presentations. This possibility is problematic, because it is becoming increasingly clear that this disorder may present with, or have, dementia as the predominant clinical feature.[33,51,88] Not unexpectedly, there is considerable overlap between the different criteria; however, although all proposals have inclusion criteria, only one has exclusion criteria.[81]

TABLE 13. *Clinical manifestations of CBD*

Reference	Clinical manifestations
Riley et al.[84]	*Basal ganglia signs* Akinesia, rigidity; limb dystonia; athetosis; postural instability, falls; orolingual dyskinesias *Cerebral cortical signs* Cortical sensory loss; alien limb phenomenon; dementia apraxia; frontal release reflexes; dysphasia *Other manifestations* Postural-action tremor; hyperreflexia; impaired ocular motility; dysarthria; focal reflex myoclonus; impaired eyelid motion; dysphagia
Watts et al.[86,87]	*Major* Akinesia, rigidity, postural/gait disturbance; action/postural tremor; alien limb phenomenon; cortical signs; dystonia; myoclonus *Minor* Choreoathetosis; dementia; cerebellar signs; supranuclear gaze abnormalities; frontal release signs; blepharospasm

Superscript numbers correspond to the list of References.
CBD, corticobasal degeneration.

Riley and Lang[82,84] were the first to propose a set of clinical manifestations (Table 13) based on literature review of 12 cases (7 pathologically confirmed) and 15 of their own cases (only 2 pathologically confirmed). Another set of manifestations was proposed by Watts and coworkers[86,87] who divided the clinical manifestations of CBD into "major" and "minor" categories (Table 13). Rinne and colleagues[85] (without mentioning diagnostic criteria), when describing a large series of 36 patients with CBD, outlined the five common types of clinical presentations. The most common presentation was with a ''useless'' arm, which could be due to any combination of rigidity; dystonia; akinesia, apraxia or "alien limb," with or without myoclonus. Other initial presentations included a similar repertoire, but affecting the leg and, thus, presenting as a gait disorder.

Lang and colleagues[81] suggested the first formal diagnostic criteria for research purposes (Table 14). However, the authors did not make qualifications about what duration of levodopa treatment constitutes "sustained." Nearly a third of patients with CBD can have some response initially to levodopa (sometimes for up to 2–3 years),[89] and diagnosis can be a problem before other signs appear to make it apparent (generally in the first

TABLE 14. *Proposed research criteria for CBD*

Reference	Inclusion criteria	Exclusion criteria
Lang et al.[81]	Rigidity plus one cortical sign (apraxia, cortical sensory loss, or alien limb) *Or* Asymmetric rigidity, dystonia and focal reflex myoclonus	Early dementia; early vertical gaze palsy; rest tremor; severe autonomic disturbances; sustained responsiveness to levodopa; lesions on imaging studies indicating another pathologic condition
Kumar et al.[80]	Chronic progressive course; asymmetric onset; presence of: "higher" cortical dysfunction (apraxia, cortical sensory loss, or alien limb); *And* Movement disorders - akinetic rigid syndrome-levodopa resistant, and limb dystonia and reflex; focal myoclonus	

Superscript numbers correspond to the list of References.

Qualification of clinical features: rigidity, easily detectable without reinforcement; apraxia, more than simple use of limb as an object, clear absence of cognitive or motor deficit; cortical sensory loss, asymmetric, with preserved primary sensation; alien limb phenomenon, more than simple levitation; dystonia, focal in limb, present at rest at onset; myoclonus, reflex myoclonus spreading beyond stimulated digits.

CBD, corticobasal degeneration.

year). A second exclusion criterion is the presence of a vertical supranuclear gaze palsy indicating PSP,[80,81] but there is no qualification about the degree or direction of the supranuclear gaze palsy. In a subsequent publication,[80] the same group tried to refine these criteria and gave frequency estimates of occurrence in each of the clinical manifestations of CBD at onset, the first 3 years, and later in the course (Table 14).[80] Finally, Riley and Lang[83] reported an unpublished classification by Maraganore and coworkers (mentioned as a personal communication) which divided clinical diagnostic certainty into possible (progressive course, asymmetric limb rigidity, or apraxia), probable (added focal or appendicular dystonia, myoclonus, or tremor), and definite (added alien limb, cortical sensory loss, and the presence of mirror movements). In a series of nine cases (reported in abstract form) using this set of criteria, only one of the nine cases clinically suspected to have CBD turned out to have the characteristic pathology. Notably, two of three patients with "probable," and both patients classified as "definite" CBD, turned out to have a different diagnosis at autopsy.[90]

Two studies have looked at the diagnostic accuracy of CBD using clinical features (but not testing any of the above criteria formally). Evaluating 10 autopsy-proven cases of CBD, Litvan and colleagues[51] found that the specificity of the diagnosis of CBD using the clinical features was very high but that the sensitivity was very low, particularly in the first 3 years as well as later on. This finding meant that CBD was underdiagnosed. The main conclusion was that limb dystonia, ideomotor apraxia, myoclonus, and asymmetric akinetic–rigid syndrome, with late onset of gait or balance disturbances, were the best predictors for the diagnosis of CBD. It is important to point out that the cases used in this study were largely obtained from movement disorders centers. Thus, patients with dementia- or aphasia-predominant phenotypes would not have been included.

Recently, Litvan and coworkers[91] studied differentiating clinical features of 51 patients pathologically diagnosed with PSP (24 cases) and CBD (27 cases) by logistic regression analysis. This method identified two sets of predictors (models) for CBD patients (Table 18). CBD patients presented with lateralized motor (e.g., parkinsonism, dystonia, or myoclonus) and cognitive signs (e.g., ideomotor apraxia, aphasia, or alien limb), whereas PSP patients often had severe postural instability at onset, symmetric parkinsonism, vertical supranuclear gaze palsy, and speech- and frontal-lobe–type features. On the other hand, CBD patients presenting with a nonmotor (termed "dementia") phenotype characterized by early severe frontal dementia and eventually bilateral parkinsonism were generally misdiagnosed.

The main role of diagnostic criteria should be to help differentiate CBD from idiopathic PD and other atypical parkinsonian disorders (mainly PSP) if the patient presents with the classic motor disorder. However, if the patient presents with dementia (as is being increasingly recognized), CBD must be differentiated from other degenerative dementing disorders with which the clinical features overlap.[90,92–98] The existing diagnostic criteria have been tailored to address mainly the former presentation. In fact, the proposals of Lang and coworkers[81] and Kumar and colleagues[80] have dementia as an exclusion feature.

None of the diagnostic criteria proposed mention specialized structural or functional imaging studies[99] or specialized electrophysiological tests.[100] These tests are not yet robust or sensitive enough to differentiate between CBD and other related conditions. Their utility will only become established after prospective studies demonstrate

good sensitivity and specificity when applied to patients in both early and later stages of the disease.

Recent Developments and Future Objectives

The challenge for any future criteria for CBD will be to address the issue of nonmotor presentation of CBD with early dementia.[101] In a recent study by Litvan and coworkers,[91] CBD cases presenting with early dementia and parkinsonism were more likely to be misdiagnosed. Grimes and colleagues[88] found that dementia was the most common presentation of CBD and a minority of patients demonstrated the "lateralized" disorder, which might be differentiated with criteria such as those outlined (Table 15).

ANCILLARY FEATURES

Ancillary laboratory tests are usually not included as diagnostic criteria and tend to be used to support a diagnosis or rule out alternative disorders. Although in neurology very few diagnoses are driven by pharmacological responses, levodopa responsiveness still has been considered to be particularly helpful in the diagnosis of PD by some authorities. Most patients, but not all, who have pathologically confirmed PD respond to levodopa during life, although responsiveness is not specific to PD.[102] Nearly a third of the patients with PSP respond incompletely to levodopa, and in MSA, this response may be particularly robust in the early months or years of disease.[103] Many of these patients remain partially responsive until death. Several authors have observed that levodopa-induced dyskinesias occur more often in PD than in the other parkinsonian disorders. However, this occurrence is not specific to PD, and patients with MSA can have severe dyskinesias that involve the craniocervical area as well as the extremities.[103] Specifically in MSA-P, frequent craniocervical dystonia in both untreated and treated patients have been reported.[104] Furthermore, a small proportion of PSP and even CBD patients also develop dyskinesias. Challenge tests with a short-acting dopaminergic drug like apomorphine or levodopa have been used to support the clinical diagnosis of early PD.[105,106] In a recent review, the accuracy of such pharmacological tests in determining the diagnosis of PD was found to be similar but not superior to the response to chronic levodopa therapy. The authors concluded that the acute testing had the advantage of rapid data acquisition but added that there is a potential for significant adverse events and cost, without direct therapeutic benefit to the patient.[107] A false-negative or a false-positive diagnosis suggests that the patient will receive an inappropriate therapy and management. According to Sackett and colleagues[108] "being told that you have a disease when you do not have it is frequently as disabling as actually having it, and almost always more disabling than not knowing that you have a disease, when you do have it."

Disturbances in olfactory function have been described in patients with PD, but the techniques needed to detect these deficits are not generally available to the practicing physician.[109] A "parkinsonian" personality has been proposed by some authors, but the lack of specificity of such personality traits (introspection, emotionally rigid, hesitant, and law-abiding) limits any applicability to diagnosis within a general population sample.[110]

There have been suggestions that careful analysis of eye movement abnormalities, which are as common in CBD as in PSP, may help with early differential diagnosis.[111] Horizontal saccadic latencies are significantly increased bilaterally in patients with CBD when compared to PSP patients. In contrast, saccadic velocity is slow, especially vertically, in PSP but normal in CBD patients. Saccades are normal in PD. The use of electrooculographic recordings may help differentiate patients with PSP and CBD from those with PD.[111,112] However, it should be kept in mind that, as of yet, there is no prospective study correlating sequential assessments of eye movements antemortem to pathological postmortem diagnosis.

TABLE 15. *Logistic regression analysis models predicting CBD vs. PSP ([91])*

Model	Predictors	Feature	Odds ratio *f*	Model
A	Asymmetric parkinsonism	11 ($P < 0.001$)	28	33 ($P < 0.0001$)
	Falls at first clinic visit	6 ($P < 0.01$)	0.1	
	Cognitive disturbances at onset	7 ($P < 0.008$)	9	
B	Cognitive disturbances at onset	11 ($P < 0.001$)	72	33 ($P < 0.0001$)
	Asymmetric parkinsonism	9 ($P < 0.002$)	36	
	Speech disturbances	8 ($P < 0.005$)	0.06	

Logistic regression analysis contributed to distinguish between 51 patients with the clinicopathologic diagnosis of PSP (n = 24) and CBD (n = 27). See text for more details. These models have not been cross-validated or evaluated in an independent sample.

CBD, corticobasal degeneration; PSP, progressive supranuclear palsy.

The data from studies using magnetic resonance imaging (MRI) suggest that, in T2 MRI scans, the presence of a hyperintense rim at the lateral border of the putamen and hypointensity in or atrophy of the putamen is relatively specific for MSA, particularly in differentiating it from PD and normal control subjects. Additionally, a recent study suggests that diffusion weighted imaging may be even more powerful than the T2 signal change in discriminating MSA-P from PD.[68] Also, although infratentorial changes can help to distinguish MSA-P from PD and other forms of atypical parkinsonism such as PSP and CBD, they cannot necessarily differentiate MSA-C from other (spino) cerebellar degenerations.[49,113–117] MRI studies show that the axial anteroposterior diameter of the midbrain (<17 mm) among other measures (dilation of the third ventricle and frontotemporal lobe atrophy) distinguished patients with PSP from those with MSA, but these distinctions were not helpful to separate PSP from CBD.[116] Studies using positron emission tomography and single photon emission computed tomography (SPECT) indicate that markers of presynaptic dopaminergic terminals (e.g., fluorodopa[118] and β-CIT[119]) cannot differentiate among PD, MSA, and PSP[120–123] but may be able to identify subjects with sOPCA who will evolve into an MSA phenotype.[75,124] Studies of striatal metabolism using fluorodeoxyglucose[118] appear able to differentiate MSA cases from control subjects and PD patients.[125,126] However, both PSP and CBD also show striatal hypometabolism, although the anatomical patterns may differ somewhat in these disorders.[127] Similarly, ligands for the dopamine D2 receptor can distinguish MSA cases from control subjects and often from PD patients,[128,129] but binding of these ligands can also be decreased in other atypical parkinsonian syndromes such as PSP.[130] Abnormalities in anal and urethral sphincter EMGs have been reported to identify with good sensitivity and specificity patients with MSA.[131,132] However, other investigators have suggested that patients with advanced PD[133,134] and PSP[135,136] may also have an abnormal sphincter EMG. A promising technique to differentiate MSA from PD with autonomic failure is the heart to mediastinal ratio in SPECT studies using [^{123}I]-meta-iodobenzylguanidine, which is structurally similar to norepinephrine and is taken up into postganglionic adrenergic neurons.[119,137] Electrophysiologic studies such as the evaluation of the auditory startle response in PSP[138,139] and myoclonus in MSA and CBD,[140] may also be helpful in distinguishing these disorders.

In summary, certain ancillary tests may help to differentiate the atypical parkinsonism disorders from PD but are less useful in distinguishing between different forms of atypical parkinsonism. Currently, diagnosis of all these diseases continues to rest on the clinical findings and the judicious use of ancillary studies.

APPENDIX

SIC Task Force for the Study of Diagnostic Criteria for Parkinsonian Disorders

Chair: Irene Litvan; Members: Kapil Sethi and Christopher Goetz, Parkinson's disease; Gregor Wenning and Ian McKeith, dementia with Lewy bodies; David Burn and Irene Litvan, progressive supranuclear palsy; Kalish Bhatia and Anthony Lang, corticobasal degeneration; Cliff Shults and Niall Quinn, multiple system atrophy.

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