Accuracy of the clinical diagnosis of corticobasal degeneration:

A clinicopathologic study

I. Litvan, MD; Y. Agid, MD, PhD; C. Goetz, MD; J. Jankovic, MD; G.K. Wenning, MD, PhD; J.P. Brandel, MD; E.C. Lai, MD; M. Verny, MD; K. Ray-Chaudhuri, MD; A. McKee, MD; K. Jellinger, MD; R.K.B. Pearce, MD; and J.J. Bartko, PhD

Article abstract—The accuracy of the clinical diagnosis of corticobasal degeneration (CBD) is unknown. To determine its diagnostic accuracy, we presented 105 cases with known neuropathologic diagnoses, including CBD (n = 10), progressive supranuclear palsy (PSP, n = 24), Parkinson's disease (n = 15), diffuse Lewy body disease (n = 14), multiple system atrophy (n = 16), postencephalitic parkinsonism (n = 7), Pick's disease (n = 7), Creutzfeldt-Jakob disease (n = 4), Alzheimer's disease (n = 4), vascular parkinsonism (n = 3), and Whipple's disease (n = 1), as clinical vignettes to six neurologists unaware of the autopsy findings. Reliability was measured with the κ statistics. The neurologists' clinical diagnoses were compared with clinicopathologic diagnoses for sensitivity, specificity, and positive predictive values at first and last clinic visits. The group reliability for the diagnosis of CBD significantly improved from moderate for the first visit (mean = 34 months after onset) to substantial for the last (68 months after onset). For the first visit, mean sensitivity for CBD was low (35%), but specificity was near-perfect (99.6%). For the last visit, mean sensitivity minimally increased (48.3%), and specificity remained stable. False-negative misdiagnoses mainly occurred with PSP. False-positive diagnoses were rare. The extremely low sensitivity of the clinical diagnosis of CBD suggests that this disorder is markedly underdiagnosed. Although the validity of the clinical diagnosis might have been improved if neurologists could have examined these patients, more important is that this disorder was misdiagnosed by the primary neurologists. In our data set, the best predictors for the diagnosis of CBD included limb dystonia, ideomotor apraxia, myoclonus, and asymmetric akinetic-rigid syndrome with late onset of gait or balance disturbances.

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Corticobasal degeneration (CBD), also called corticodentatonigral degeneration with neuronal achromasia[1] and cortical-basal ganglionic degeneration,[2] presents in the sixth or seventh decade with a slowly progressive, unilaterally jerky, tremulous, akinetic, rigid, and apraxic limb held in a fixed dystonic posture and displaying the alien limb syndrome.[1-3] However, symptoms and presentations vary. The behavioral manifestations in CBD may also include language disturbances and frontal-lobe–type behavior.[4-6] The clinical picture may also include postural instability, athetosis, focal stimulus-sensitive myoclonus, action tremor, cortical sensory loss, supranuclear gaze palsy, Babinski signs, and pseudobulbar palsy.[1-3,7-9] Thus, CBD shares many clinical symptoms with several other neurodegenerative disorders, including Parkinson's disease (PD), progressive supranuclear palsy (PSP), multiple system atrophy, and Pick's disease.[9-12] The accuracy of neurologists in diagnosing CBD is unknown. Since there are no absolute markers for the clinical diagnosis of CBD, neuropathology remains the "gold standard" for its diagnosis,[13,14] even if there may be overlap and difficulties in the morphologic differentiation of CBD from PD and PSP.[11,15,16]

The objective of the present study was to determine the accuracy of the clinical diagnosis of CBD judged by the neurologists' diagnostic reliability and by validating clinical findings with pathologic information.

Methods. *Sample and data collection.* One hundred five cases with a clinical diagnosis of parkinsonism or dementia were chosen because of shared clinical features with CBD. The cases met the National Institute of Neurological Disorders and Stroke (NINDS) neuropathologic criteria for the diagnosis of PSP and related disorders[17] and Kosaka's

From the Neuroepidemiology Branch (Dr. Litvan), National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD; the Fédération de Neurologie and INSERM U 289 (Drs. Agid and Brandel), Hôpital de la Salpêtrière, Paris, France; Department of Neurology (Dr. Goetz), Rush Medical College, Chicago, IL; Department of Neurology (Drs. Jankovic and Lai), Baylor College of Medicine, Houston, TX; the Parkinson's Disease Society Brain Tissue Bank (Drs. Wenning and Pearce), Institute of Neurology, London, UK; Department of Neurology (Dr. Ray-Chaudhuri), Institute of Psychiatry, London, UK; the Raymond Escourolle Neuropathology Laboratory (Dr. Verny), INSERM U 360, Hôpital de la Salpêtrière, Paris, France; Department of Neuropathology (Dr. McKee), Massachusetts General Hospital, Boston, MA; the Ludwig Boltzmann Institute of Clinical Neurobiology (Dr. Jellinger), Vienna, Austria; and Division of Epidemiology and Research Studies (Dr. Bartko), National Institute of Mental Health, Bethesda, MD.

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Address correspondence and reprint requests to Dr. Irene Litvan, Federal Building, Room 714, National Institute of Neurological Disorders and Stroke, National Institutes of Health, Bethesda, MD 20892-9130.

Table 1 *Demographic characteristics of the sample*

Disorder (n = 105)	Age at onset (yr)	Time to first visit (mo)	Time between visits (mo)
Corticobasal degeneration (n = 10)	62 ± 3	34 ± 8	34 ± 7
Progressive supranuclear palsy (n = 24)	62 ± 1	45 ± 6	28 ± 4
Multiple system atrophy (n = 16)	55 ± 2*	45 ± 8	26 ± 5
Parkinson's disease (n = 15)	53 ± 3*	77 ± 22*	98 ± 17*
Diffuse Lewy body disease (n = 14)	68 ± 3	37 ± 10	48 ± 17
Pick's disease (n = 7)	64 ± 4	53 ± 13	25 ± 10
Postencephalitic parkinsonism (n = 7)	42 ± 4*	126 ± 32*	187 ± 54*
Alzheimer's disease with parkinsonism (n = 4)	81 ± 4*	44 ± 16	32 ± 14
Creutzfeldt-Jakob disease (n = 4)	62 ± 3	3 ± 1*	2 ± 1*
Vascular parkinsonism (n = 3)	71 ± 5	20 ± 14	47 ± 24
Whipple's disease (n = 1)	52	8	44

Values are mean ± SEM except for Whipple's disease.

*$p < 0.05$ for the comparison with the other groups for ages or times.

criteria for Lewy body disease.[18] Cases were selected from research and clinical files by experienced neuropathologists who had at least 75% diagnostic certainty. Cases were collected between 1993 and 1994, and had to have had complete neurologic examinations for the first and last clinic visits. The same sample was previously used in a study on the accuracy of clinical criteria for the diagnosis of PSP.[12] Demographic characteristics of the patients are shown in table 1. As previously reported,[12] the case records were abstracted on standardized forms by neurologists who were unaware of the neuropathologic diagnoses and who were instructed to follow predefined procedures. Cases were summarized and presented as clinical vignettes in randomized order to six raters (three junior and three senior neurologists with particular interest in movement disorders) who were unaware of the clinical design of the study. No specific diagnostic criteria were provided. Clinical vignettes included demographic data, history of present and past illness, therapies, family history, physical and neurologic examinations, and clinical laboratory studies. After reading the information from the first visit, raters completed a standardized form offering their own diagnoses and specifying the main features they used for their clinical decisions. They then evaluated the last visit and suggested a final diagnosis.

Reliability. To measure group agreement beyond chance, we chose the generalized κ statistics.[19-21] Like a correlation coefficient, κ varies from −1.0 (complete disagreement) to 0 (chance agreement) to +1.0 (perfect agreement). Strength of agreement is designated poor (κ < 0), slight (κ = 0 to 0.20), fair (κ = 0.21 to 0.4), moderate (κ = 0.41 to 0.60), substantial (κ = 0.61 to 0.80), and near-perfect to perfect (κ = 0.81 to 1.0), as previously suggested.[22]

Validity. We compared the neurologists' diagnoses with the neuropathologic diagnosis to measure sensitivity, specificity, and predictive values at first and last clinic visits (see Appendix for definitions).[23] A low prevalence of CBD in this population was intentionally chosen to mirror closely what neurologists experience in their practice. There were a total of 630 observations (105 cases × 6 raters).

Comparison of accuracy measures. The pooled κ test was used to determine the significance between κ values,[24] the Cochran Q test to evaluate differences in sensitivity and specificity between raters,[23] and the McNemar test to evaluate the differences in sensitivity and specificity between visits.[25]

Variables for prediction of CBD. Logistic regression analysis was performed to identify the variables that could best predict the autopsy-confirmed cases of CBD. The variables used in the analysis were all the main variables the neurologists used to make their clinical decision (features recorded on a standardized form when they evaluated the clinical vignettes). A separate analysis was performed for each of the six raters for both the first and last visits.

Results. *Reliability.* Group agreement for the diagnosis of CBD significantly improved from moderate (κ = 0.52) for the first visit to substantial (κ = 0.71) for the last (pooled κ test, $p < 0.0001$). For the first visit, senior neurologists achieved better agreement (κ = 0.63) than junior neurologists (κ = 0.31) (pooled κ test, $p < 0.0001$), but there was no significant difference between junior (κ = 0.7) and senior neurologists (κ = 0.69) for the last visit. Agreement between junior neurologists significantly improved for the last visit (pooled κ test, $p < 0.00001$).

Validity. For the first visit, sensitivity for the diagnosis of CBD for each rater was low (mean, SD, 35 ± 21%), but specificity was near-perfect (99.6 ± 0.6%) (figure). For the last visit, sensitivity minimally increased (48.3 ± 7.5%) and specificity remained stable (see figure). For both visits, the positive predictive values (94 ± 9%; range, 80 to 100%) were high.

Raters' sensitivity varied at the first visit ($p < 0.01$, Cochran Q); overall, senior neurologists identified more cases than juniors. There was no difference in sensitivity between first and last visits for any rater.

The sensitivity for the diagnosis of CBD by primary neurologists (who clinically followed up these patients) was very low for both the first (20%) and last (30%) clinic visits, but the specificity was high (100%).

Misdiagnoses. For the first visit, false-negative misdiagnoses occurred in 65% of the 60 CBD observations (10

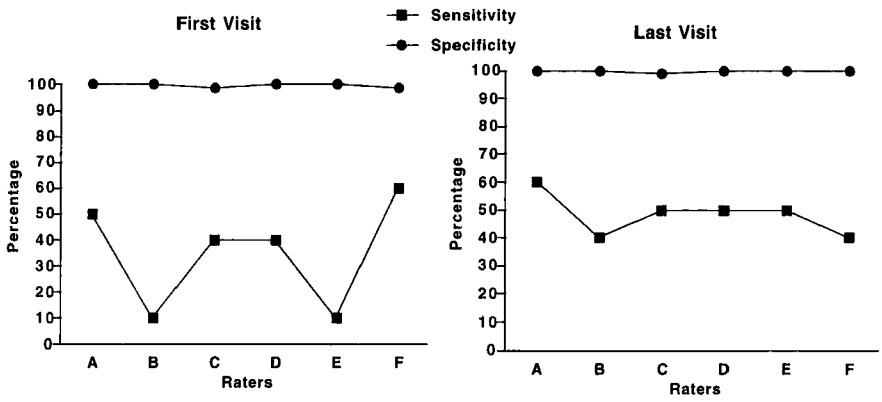

Figure. Comparison of sensitivity and specificity for the diagnosis of corticobasal degeneration for the first and last visits.

CBD cases × 6 raters), mainly with PSP (33% of the misdiagnoses), but also with vascular parkinsonism (15%), PD (13%), multiple system atrophy (10%), Pick's disease (8%), Alzheimer's disease with extrapyramidal features (8%), and other disorders (13%). False-positive diagnoses were rare (9% of the observations clinically diagnosed as CBD) and occurred with diffuse Lewy body disease and PD. For the last visit, false-negative misdiagnoses (52% of the 60 CBD observations) occurred mainly with PSP (42% of the misdiagnoses), but also with vascular parkinsonism (23%), Alzheimer's disease with extrapyramidal features (13%), PD (6%), multiple system atrophy (6%), and other disorders (10%). False-positive diagnoses were rare (6% of the observations clinically diagnosed as CBD) and occurred with Alzheimer's disease with extrapyramidal features and multiple system atrophy (striatonigral-degeneration type).

Variables for prediction of CBD. The best predictors for the diagnosis of CBD for each rater are presented in table 2. The logistic regression analysis identified one to three features for each rater (raters A–F) that significantly predicted autopsy-confirmed CBD (e.g., for rater A, limb dystonia and absence of balance disturbances). Overall, the best predictors at the first visit included absence of gait or balance disturbance (identified by raters A, B, C, D, and E), limb dystonia (raters A, B, D, and F), asymmetric

Table 2 *Predictors for the diagnosis of corticobasal degeneration*

Rater	Predictors	Parameter χ^2	Odds ratio*	Model χ^2
First visit				
A	Limb dystonia	6.2 ($p < 0.01$)	12 (1.6–95)	12 ($p < 0.002$)
	No balance disturbance	4.5 ($p < 0.03$)	5 (1.2–31)	
B	No gait disturbance	5.3 ($p < 0.02$)	6.3 (1.3–34)	12.6 ($p < 0.001$)
	Limb dystonia	3.9 ($p < 0.05$)	7.5 (1.0–57)	
C	No gait disturbance	6.3 ($p < 0.01$)	6.3 (1.5–24.2)	6.3 ($p < 0.01$)
D	No gait disturbance	5.4 ($p < 0.01$)	8.7 (1.6–73)	17.9 ($p < 0.0005$)
	Limb dystonia	5 ($p < 0.02$)	16.4 (1.5–239)	
	Ideomotor apraxia	4.8 ($p < 0.02$)	11.2 (1.2–121)	
E	Asymmetric parkinsonism	7.5 ($p < 0.006$)	8 (1.9–42)	13.7 ($p < 0.001$)
	No gait disturbance	4.6 ($p < 0.03$)	5.1 (1.2–23)	
F	Limb dystonia	8.8 ($p < 0.002$)	21 (3–190)	8.8 ($p < 0.002$)
Last visit				
A	Ideomotor apraxia	8.1 ($p < 0.004$)	10.5 (2–56)	12.5 ($p < 0.001$)
	Late balance disturbance	5.1 ($p < 0.02$)	6 (1.2–30)	
B	Late gait disturbance	18 ($p < 0.0001$)	29 (6–171)	20.2 ($p < 0.0001$)
	Focal myoclonias	3.8 ($p < 0.05$)	29 (1.0–884)	
C	Early cognitive disturbance	7.1 ($p < 0.007$)	13 (2.1–84)	7.1 ($p < 0.007$)
E	Ideomotor apraxia	14 ($p < 0.0002$)	45 (6.8–410)	18.5 ($p < 0.0001$)
	Early cognitive disturbance	6.7 ($p < 0.009$)	14 (1.6–121)	
F	Limb dystonia	11 ($p < 0.0008$)	20 (3.7–126)	11 ($p < 0.0007$)

Separate logistic regression analysis for each rater. No predictors were identified for rater D for the last visit.

* Lower and upper 95% odds ratio.

parkinsonism (rater E), and ideomotor apraxia (rater D). For the first visit, the best model was one of rater D, which consists of absence of gait disturbance, limb dystonia, and ideomotor apraxia ($p < 0.0005$). The best predictors at the last visit were late balance or gait disturbance (raters A and B), ideomotor apraxia (raters A and E), early cognitive disturbance (rater C), focal myoclonias (rater B), and limb dystonia (rater F).

Discussion. *Study limitations.* Although the present study has some limitations, they are the limitations of the field and do not invalidate the conclusions. For example, autopsy studies from which we selected our population may include more atypical patients than those who are usually seen in medical practice. However, the demographics of our patients are similar to those of previous clinical studies on CBD.[2,3] Moreover, clinically based studies may include disorders that can mask CBD. Disorders like Alzheimer's disease,[26,27] PSP,[10,28] Pick's disease,[10,29] hemiatrophy parkinsonism,[30] and striatonigral degeneration[31] may completely satisfy the "CBD syndrome." These diseases occasionally share with CBD several features (ideomotor apraxia, myoclonus, focal dystonia, pronounced asymmetry) that make them indistinguishable in life from autopsy-confirmed "CBD disease." In addition, it may be difficult to clinically identify when CBD overlaps with AD.[32] Thus, at the present time, autopsy is required to confirm the diagnosis.

To decrease the impact of the complexity of the neuropathologic diagnosis, however, we chose cases in which pathologists had 75% or greater diagnostic certainty. Since there are difficulties not only in the clinical but also in the neuropathologic diagnosis of CBD,[11,14-16,33] one can argue that CBD may not be a separate nosologic entity. Some neuropathologic cases of CBD may be difficult to distinguish from PSP, because the basophilic inclusions of CBD are often indistinguishable from neurofibrillary tangles, and clear cytoskeletal abnormalities are found in both CBD and PSP.[15,34] Neuropathologically, some cases may also be difficult to differentiate from Pick's disease, as both disorders may have ballooned cells, astrogliosis, and neuronal loss.[11,15] However, the biochemical tau profiles of CBD differ from those of AD, PSP, and Pick's disease.[16,35,36] CBD may present characteristic "astrocytic plaques" (tau accumulates in the distal astrocytic process creating the image of a plaque)[37] and ubiquitin-positive achromatic neurons,[38] instead of ubiquitin-negative, tau-positive achromatic neurons found in Pick's disease.

We needed multicenter collaboration to obtain the required sample size, but the seven medical centers providing the cases specialize in evaluating these types of disorders. In spite of the stringent inclusion criteria of our study, the retrospectively collected data were never complete. For instance, data on levodopa efficacy were missing in most of our CBD cases. Although lack of appropriate response to levodopa therapy often indicates atypical parkinsonism, in practice, dopaminergic therapy may not be administered when parkinsonian symptoms are not troublesome or when severe dystonia is present. Moreover, features suggesting ideomotor apraxia, a key finding for the diagnosis of CBD, were not always appropriately described in the records, since it is rather complex to evaluate learned motor skill behaviors of subjects who exhibit akinesia, rigidity, and dystonia.[39] Similarly, sensory examination findings, usually reported as normal, may not have included cortical sensory loss. Only prospectively collected data will allow investigators to minimize these problems and identify other features such as visual field or sensory inattention found in our practice and occasionally in the literature associated with CBD but rarely routinely searched for by neurologists.[2,40-42]

The CBD sample size, intentionally chosen to reflect the rarity of this disorder, would not allow us to choose a calibration sample, different from the testing sample, for the logistic regression analysis. Thus, our predictive variables are preliminary findings and will need to be tested in an independent and prospectively collected sample. However, the predictive features identified in our study are generally in agreement with characteristic features identified in previous studies involving larger samples.[3]

Reliability. Agreement among the neurologists for the clinical diagnosis of CBD significantly improved from moderate for the first clinic visit to substantial for the last visit. Senior neurologists achieved significantly higher agreement for the diagnosis of CBD for the first visit than did junior neurologists, but both groups achieved a substantial agreement for the last visit. Variability among the neurologists may be explained by degree of experience in evaluating atypical parkinsonian cases. It may also be explained by differences in interpretation of clinical phenomena. The diagnosis of CBD seems to be more difficult than that of PSP. These same raters achieved a higher interrater agreement for the diagnosis of PSP ($\kappa = 0.65$ to 0.81), and junior and senior neurologists performed similarly.[12] Nevertheless, perfect agreement may not reflect diagnostic accuracy; in fact, raters may all agree but be mistaken.

Validity. In general, the validity measures are better at reflecting diagnostic accuracy. The raters identified very few cases of CBD (very low sensitivity) but correctly rejected non-CBD cases (excellent specificity and positive predictive value for the clinical diagnosis of CBD). The extremely low sensitivity for the clinical diagnosis of CBD suggests that this disorder is severely underdiagnosed. In general, the junior neurologists benefitted from the presence of more features to make the diagnosis of CBD, but symptom duration was not relevant for the diagnosis of the senior neurologists, who were able to identify patients with CBD at an earlier stage (34 months after onset).

Our findings also suggest that the neurologists

tended to diagnose CBD when the clinical presentation was relatively "classic." False-positive diagnoses (cases without autopsy-confirmed CBD but incorrectly identified as such) were rare and at early stages occurred with diffuse Lewy body disease and PD, and at later stages with Alzheimer's disease with extrapyramidal features and striatonigral degeneration. Asymmetric parkinsonism and absence of gait disturbance at onset are features that CBD shares with PD, but patients with this latter disorder respond very well to levodopa therapy.[43] Multiple system atrophy, particularly when it presents without autonomic failure, may be difficult to differentiate. Nevertheless, later age at presentation, severe limb dystonia, ideomotor apraxia, cortical sensory deficits, and delayed onset of gait and balance disturbances should help differentiate CBD from multiple system atrophy.[31,44,45] Alzheimer's disease may present with ideomotor apraxia, myoclonus, extrapyramidal features, and, rarely, with alien hand syndrome.[26] However, ideomotor apraxia in Alzheimer's disease is associated with severe memory deficit,[46] and the myoclonus is usually of later onset.

False-negative diagnoses (autopsy-confirmed CBD cases falsely diagnosed as other disorders) were quite frequent, and presentations with ophthalmoplegia and extrapyramidal features were usually diagnosed as PSP. However, PSP patients usually present with a symmetric akineto-rigid parkinsonian syndrome and early postural instability and falls.[47-49] Three CBD cases, one of which has been previously described,[50] were misdiagnosed by all the raters. The course and symptomatology of two of these cases were similar to those of PSP, including the presence of vertical supranuclear palsy with downward gaze abnormalities and postural instability with unexplained falls. Moreover, these cases did not present alien hand syndrome, dystonia, myoclonus, aphasia, or limb apraxia. Previous single case reports also pointed to the difficulty of clinically differentiating PSP from CBD.[28] In our study, as also previously reported,[10,29] Pick's disease, particularly the parietal form, was misdiagnosed as CBD, since both disorders may present with similar "parietal type" symptomatology. On the other hand, both disorders can also present with severe frontal-lobe–type dysfunction.[51,52] CBD was also misdiagnosed as Alzheimer's disease with extrapyramidal features. This finding suggests that presentations with initial behavioral manifestations tend to be misdiagnosed as other dementias. Dementia and aphasia have only recently been widely recognized as possible initial presentations of CBD.[4,5,53] Earlier reports emphasized the absence of cognitive decline.[1,54,55]

Another disorder with which CBD cases are often confused was vascular parkinsonism. Unfortunately, because of difficulties in obtaining cases of pathologically confirmed vascular parkinsonism, our data set included only three cases. This small sample size may have limited our ability to identify features that could differentiate both disorders. Differentiation of CBD and vascular parkinsonism may be difficult because patients with both disorders may present with focal neurologic signs, cognitive impairment, and parkinsonism. However, a steady and slow disease course, involvement of both upper and lower limbs, presence of myoclonus, dystonia, absence of paresis, and lack of strokes should aid in the differentiation of CBD from vascular parkinsonism.[43] Autopsy-confirmed CBD cases were also misdiagnosed as striatonigral degeneration and PD. Like CBD, striatonigral degeneration may present with a levodopa-unresponsive akineto-rigid asymmetric parkinsonism and pyramidal signs.[31]

False-negative misdiagnoses are of concern because they make the task of recruiting patients with CBD difficult and impair the study of PSP with which CBD is most often confused. Although the accuracy of the diagnosis might have been improved if the neurologists could have examined the patients, this disorder was also misdiagnosed by the primary neurologists even at the last clinic visit. Although our raters had to rely on the examination findings of the primary neurologists to make their diagnoses, they diagnosed other disorders such as pathologically confirmed postencephalitic parkinsonism with a high degree of accuracy (unpublished data). Moreover, several studies suggest that the reliability of the diagnosis made by neurologists who directly examine patients[56,57] is similar to that of those who rely on clinical vignettes.[58,59]

Best predictors for the diagnosis. The best predictors for the diagnosis of CBD, at the first visit, included limb dystonia, asymmetric parkinsonism, ideomotor apraxia, and absence of balance or gait disturbances. Limb dystonia in patients with no response to levodopa treatment should strongly suggest CBD. However, there are a few cases of autopsy-confirmed PSP with limb dystonia, although it was usually not severe.[48,60-62] Similarly, a distinct asymmetric akineto-rigid parkinsonism not benefitting from levodopa therapy and the absence of early balance and gait disturbances are key features for differentiating CBD from PD, PSP (balance disturbance is often present at onset in PSP), and striatonigral degeneration.[31]

Severe ideomotor apraxia (even if not detailed enough in our study) and alien limb syndrome (not many cases in our data set had alien limb syndrome but none of the non-CBD cases had it) should also point to the diagnosis of CBD.[39] The apraxia of CBD patients is asymmetric and, particularly in the early stages, with spared mental representation of gestures, suggesting involvement of the supplementary motor area, in contrast to that found in Alzheimer's disease, which involves the parietal area.[6,39,63] CBD patients may also present ideatory apraxia[6,39] and the controversial "limb-kinetic apraxia."[64] Alien limb syndrome, when present, assisted our raters in the diagnosis of CBD.

The best predictors during the later stage of illness in our study included delayed onset of balance

and gait disturbances, ideomotor apraxia, early cognitive disturbance, and focal myoclonias. Previous reports also suggested that stimulus-sensitive myoclonus,[7,8,65] and moderate fronto-subcortical deterioration[6] are characteristic of CBD.

Conclusion. The present study shows an extremely low sensitivity in the clinical diagnosis of CBD, not only by the raters but also by the primary neurologists who examined these patients in the tertiary centers. We hope that the predictors for the diagnosis of CBD identified in our sample, an asymmetric akinetic-rigid syndrome with late-onset gait or balance disturbance, jerky limb dystonia, and early cognitive symptoms, including ideomotor apraxia, may help increase the recognition and improve the diagnostic accuracy of this disorder. The addition of laboratory data (e.g., neuroradiology, electrooculographic assessment) may also improve the accuracy of the diagnosis of CBD.[66-73] Other features that may support the diagnosis of this disorder are distinct asymmetry of sulci in the parietal region on CT or MRI,[66,67] asymmetry of cortical and subcortical fluorodeoxyglucose metabolism on PET,[68-71] perfusion asymmetry of parietal cortical regions on HMPAO SPECT,[72] reduced basal ganglia IBZM uptake on SPECT,[42] decreased horizontal saccade latency on oculography,[73] short-latency reflex myoclonus, absence of back averaged cortical potentials preceding the action myoclonus, or abnormal magnetostimulation of the motor cortex.[8,65]

Appendix *Definitions of terms used in the statistical analysis*

	Pathologic diagnosis +	Pathologic diagnosis −
Rater diagnosis +	A	B
Rater diagnosis −	C	D

Sensitivity: what proportion of patients with autopsy-confirmed corticobasal degeneration (CBD) are clinically diagnosed as having CBD? (A/A+C)
Specificity: what proportion of patients without autopsy-confirmed CBD are clinically diagnosed as not having it? (D/D+B)
Positive predictive value: what proportion of patients clinically diagnosed as having CBD truly have it? (A/A+B)
Negative predictive value: what proportion of patients clinically diagnosed as not having CBD truly do not have it? (D/C+D)

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