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Clinical features differentiating patients with postmortem confirmed progressive supranuclear palsy and corticobasal degeneration

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Abstract Progressive supranuclear palsy (PSP) and corticobasal degeneration (CBD) are often clinically confused with each other because they share a rapid disease progression, parkinsonism that responds poorly or transiently to levodopa therapy, and associated signs (e.g., ocular abnormalities, pyramidal signs and cognitive involvement). To improve the accuracy in diagnosing these disorders, this study examined the clinical features of 51 patients pathologically diagnosed with PSP and CBD. Logistic regression analysis identified two sets of predictors (models) for CBD patients, one consisting of asymmetric parkinsonism, cognitive disturbances at onset and instability and falls at first clinic visit, and the other one of asymmetric parkinsonism, cognitive disturbances at symptom onset and speech disturbances. While PSP patients often had severe postural instability at onset, symmetric parkinsonism, vertical supranuclear gaze palsy, speech and frontal lobe-type features, CBD patients presented with lateralized motor (e.g., parkinsonism, dystonia or myoclonus) and cognitive signs (e.g., ideomotor apraxia, aphasia or alien limb). On the other hand, CBD patients presenting with an alternate phenotype characterized by early severe frontal dementia and bilateral parkinsonism were generally misdiagnosed. PSP patients without vertical supranuclear gaze palsy were misdiagnosed. Recognizing the features which differentiate these disorders and the less obvious disease presentations as well as developing an increased index of suspicion will improve the diagnostic accuracy of these disorders.

Key words Progressive supranuclear palsy · Corticobasal degeneration · Diagnosis · Clinical

Introduction

As there are no biologic markers for the clinical diagnosis of parkinsonian disorders, progressive supranuclear palsy (PSP, also called Steele-Richardson-Olszewski syndrome) and corticobasal degeneration (CBD) are often clinically confused with each other and with Parkinson's disease (PD) [14, 15]. PSP and CBD have a rapid disease progression, respond only poorly or transiently to levodopa therapy, and are associated with signs not present in PD, such as ocular abnormalities, pyramidal signs and cognitive involvement. Clinicopathologic studies show that less than two-thirds of patients with PSP and less than one-half of those with CBD are diagnosed premortem by primary neurologists [14, 15]. Moreover, it takes nearly half of the disease course to diagnose these disorders. Thus, it is not surprising that the prevalence of PSP, the only one estimated, is lower than expected when incidence and survival estimates are considered [5, 8, 12].

We hypothesized that both the lack of biologic markers for their diagnosis as well as clinicians' unfamiliarity with the typical and atypical features are the major obstacles for accurately diagnosing PSP and CBD. To improve diagnostic accuracy at the beginning of the disease, the early clinical features of patients with PSP and CBD are compared on the basis of retrospectively evaluating the medical records of patients pathologically confirmed. In addition, to better understand the difficulties that primary neurologists face diagnosing these disorders, the features of patients never diagnosed clinically premortem are contrasted with those who were diagnosed.

Methods

Fifty-one patients with the clinicopathologic diagnosis of PSP (n = 24) and CBD (n = 27) fulfilling the National Institute of Neurological Disorders and Stroke (NINDS) neuropathologic criteria [6] and having detailed medical histories were selected from research and clinical neuropathological files of nine medical centers in five countries (Austria, Canada, England, France, and the United States). The PSP and CBD patients had been previously independently reported [17, 19]. The patients' records were abstracted on standardized forms by neurologists who followed strict instructions. Signs or symptoms were recorded as missing data if they were not mentioned in the records. Since the data were retrospectively collected, it was assumed that neurologists performed complete examinations and considered a feature (for example, supranuclear gaze disturbance) was absent when the examination was reported to have been "within normal limits" (for example, oculomotor function). Analysis of variance, χ^2 and logistic regression analysis were used as appropriate.

Table 1 Study group demographics

	PSP (n = 24)	CBD (n = 27)
Gender	9 F/15 M	14 F/13 M
Age onset (yrs)	62.8 ± 1.4	63.5 ± 1.4
Age at death	69.4 ± 1.4	70.5 ± 1.3
Survival (yrs)	6.6 ± 0.6	7 ± 0.6
Time to first clinical examination	3.7 ± 0.4	2.9 ± 0.4

Data presented as mean ± SEM. No between-group statistical differences

Results

There were no between-group differences in demographics (Table 1). Logistic regression analysis identified two models that contributed to distinguish these disorders and predicted a diagnosis of CBD. One included asymmetric parkinsonism, cognitive disturbances at symptom onset, and instability and falls at first clinic visit. The other one included asymmetric parkinsonism, cognitive disturbances within the first year of symptom onset, and speech disturbances at first clinic visit (Table 2). Additional features distinguishing these disorders but not entering in the models included vertical supranuclear gaze palsy ($p < 0.0005$), gait disturbances at first visit ($p < 0.001$), falls within the first year of symptom onset ($p < 0.001$), and limb apraxia ($p < 0.005$).

There were no significant differences in demographics between patients clinically misdiagnosed and those accurately

Table 2 Features predicting CBD

Model	Predictors	Feature χ	Odds ratio*f*	Model χ
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 ($p < 0.008$)	19	
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 models predicting CBD vs PSP

Table 3 Features at the first visit in PSP and premortem clinical diagnosis

Features at first visit #		Pathologically confirmed PSP (n = 24) Clinically diagnosed	Clinically misdiagnosed
Supranuclear vertical gaze palsy*	Yes (n = 18)	18	0
	No (n = 6)	3	3
Symmetric parkinsonism*	Yes (n = 21)	20	1
	No (n = 3)	1	2
Cognitive disturbances at onset	Yes (n = 2)	2	0
	No (n = 22)	19	3

*$p < 0.05$; # Features not recorded in the chart were considered absent

diagnosed. Supranuclear vertical gaze palsy, considered a cardinal feature of PSP, was not present or not documented in the three patients who were never diagnosed in life as having PSP ($p < 0.0001$) (Table 3). Moreover, all but one patient with clinically accurately diagnosed PSP had a documented vertical supranuclear gaze palsy at the last clinical visit. Two of the three misdiagnosed PSP patients had a unilateral asymmetric parkinsonism and one had a unilateral dystonia ($p < 0.05$) present at the last visit. Common features of CBD are thought to include asymmetric parkinsonism, dystonia, myoclonus and ideomotor apraxia. We found that 10 of the 15 CBD patients misdiagnosed did not have an asymmetric parkinsonism ($p < 0.05$) (Table 4). However, neurologists misdiagnosed 5 of 14 CBD patients exhibiting an asymmetric parkinsonism and were able to diagnose only 3 of 13 without it. Similarly, they misdiagnosed 10 of 13 CBD patients who had cognitive disturbances at onset ($p < 0.05$). Five of the 15 misdiagnosed CBD patients had no cognitive disturbances at onset. Twelve of the 15 misdiagnosed patients had cognitive disturbances at the first clinic visit without exhibiting an akinetic rigid syndrome ($p < 0.05$). In addition, misdiagnosed CBD patients exhibited memory disturbances (n = 10), disorientation (n = 8), personality changes (n = 8) and pyramidal signs (n = 6) ($p < 0.05$). Neurologists were unable to diagnose 13 CBD patients who lacked ideomotor apraxia at the first visit but accurately diagnosed 7 of 9 CBD patients with ideomotor apraxia ($p < 0.01$), misdiagnosed only one patient exhibiting the alien limb sign but 14 without this feature ($p < 0.01$). None of the patients with focal myoclonus (n = 4) were misdiagnosed. In addition, none of the 15 misdiagnosed CBD patients were reported to exhibit myoclonus ($p < 0.005$), 13 did not show unilateral dystonia, and 10 had a symmetric motor involvement ($p < 0.05$). The presence of dementia at later stages did not significantly influence the diagnosis.

Table 4 Features at first visit in CBD and premortem clinical diagnosis

Features at the first visit #		Pathologically confirmed CBD (n = 27) Clinically diagnosed premortem	Clinically misdiagnosed premortem
Asymmetric parkinsonism*	Yes (n = 14)	9	5
	No (n = 13)	3	10
Dystonia unilateral*	Yes (n = 8)	6	2
	No (n = 19)	6	13
Focal myoclonus*	Yes (n = 4)	4	0
	No (n = 23)	8	15
Cognitive disturbances at symptom onset*	Yes (n = 13)	3	10
	No (n = 14)	9	5
Dementia (DSM III criteria)	Yes (n = 12)	4	8
	No (n = 15)	8	7
Remote memory disturbance*	Yes (n = 13)	3	10
	No (n = 14)	9	5
Ideomotor apraxia*	Yes (n = 9)	7	2
	No (n = 18)	5	13
Alien limb*	Yes (n = 6)	5	1
	No (n = 21)	7	14

*$p < 0.05$; # Features not recorded in the chart were considered absent

Discussion

This study shows that the presence of asymmetric parkinsonism, cognitive disturbances at onset, but absence of falls predicted CBD, whereas absence of cognitive disturbances at onset, presence of symmetric parkinsonism and falls at the time of the first visit predicted PSP. In fact, as previously described [5, 8, 12, 15, 19], PSP usually presented in the elderly with early postural instability and tendency to falls followed by a peculiar wide-based, slow and unsteady gait, and preserved associated movements. Supranuclear gaze palsy, a feature that assists in distinguishing PSP from CBD, was not an early differentiating sign. This is not surprising because supranuclear gaze palsy is rarely present at the onset of PSP, but usually develops 3 to 4 years later or, as in 3 of our cases it was never noted in life. Moreover, the absence of vertical supranuclear gaze palsy at the last visit significantly determined PSP misdiagnosis. It is possible that oculomotor abnormalities may be present earlier if neurologists evaluated speed and latency of saccades. Recent observations suggest that slowing of vertical saccades precedes the supranuclear vertical gaze palsy observed in PSP [22]. In contrast, CBD patients show normal saccadic velocity but increased latency of saccades [22]. Furthermore, CBD patients may exhibit an "oculomotor apraxia", that is, they have difficulty in initiating vertical and horizontal voluntary gaze but have preserved pursuit, saccades and optokinetic nystagmus. Although supranuclear gaze palsy is a key diagnostic feature of PSP, occasionally it is present in patients with dementia with Lewy bodies, multiple system atrophy, arteriosclerotic pseudoparkinsonism, Creutzfeldt-Jakob disease, and Whipple's disease [1, 16]. In PSP, however, the oculomotor abnormality affects vertical gaze first and then horizontal gaze, ruling out most of these diseases.

PSP patients' parkinsonism in this study group was characterized by symmetric limb signs, axial more than limb involvement, and lack of benefit from levodopa therapy. Asymmetric parkinsonism, when present, favors CBD over PSP and PD over PSP [16]. Moreover, the differential diagnosis between PSP and PD should be straightforward in patients who present with early gait and postural disturbances [16]. PSP patients showed early postural instability, whereas in PD patients, such instability may not develop until 9 to 12 years later [11]. Falls at the first visit were a significant feature differentiating PSP and CBD patients from each other. Moreover, while CBD patients who suffered repeated falls had an asymmetric involvement of the lower extremity, PSP patients who fall, have symmetric limb involvement ($p < 0.001$).

As previously reported [6, 19, 21], none of the PSP patients included in this study had symptoms before age 40, a disease duration longer than 20 years, severe autonomic dysfunction, delusions or hallucinations unrelated to levodopa or focal cognitive features (aphasia, visual or sensory hemineglect).

PSP patients usually exhibit early florid frontal lobe symptomatology (e.g., concrete thought, difficulty shifting concepts, perseveration or behavioral disturbances, including apathy, disinhibition, depression, and anxiety) [7, 9, 18], but cognitive disturbances at symptom onset characterized patients with CBD. Cognitive disturbances in CBD typically consisted of either lateralized disturbances (aphasia, apraxia) or frontal dementia associated with aphasia and attentional disturbances. The present findings agree with the features delineated in the NINDS and Society for PSP, Inc. (SPSP) criteria [13]. Although most PSP patients in this study exhibited symmetric limb involvement, one patient had focal limb dystonia, as previously described [3]. None of the PSP patients of this study exhibited limb levitation [2], which in addition to focal dystonia are major challenges to the diagnosis.

Patients with CBD presenting with a unilateral jerky, tremulous, akineto-rigid and apraxic extremity held in a fixed dystonic posture and displaying the alien limb syndrome were more likely to be accurately diagnosed. Clumsiness of one hand and arm with loss of manual dexterity in performance of fine motor tasks, secondary to ideomotor apraxia, was a key finding for the diagnosis of CBD. Falls, in CBD, rarely occur early, usually occurring late in the course, in contrast with PSP. Gait problems at disease onset in CBD usually occurred in association with asymmetric involvement. Asymmetric symptoms tended to remain distinctly asymmetric, when spreading from the affected limb to the ipsilateral limb, or even to the corresponding contralateral limb. Speech disturbances were infrequently early complaints.

Neurologists had difficulties diagnosing patients with early frontal dementia without alien hand syndrome, ideomotor apraxia, asymmetric parkinsonism and unilateral dystonia. This may be related to existing confusion in the diagnosis of CBD. What was diagnosed pathologically as Pick's disease with few or no Pick bodies (Pick disease Type B) decades ago [20], is currently undergoing reclassification as CBD, although it is not universally accepted. Physicians in many centers, confronted clinically with a patient with early and prominent cognitive decline or pathologically with the recently broadened criteria of CBD [4], would make the diagnosis of Pick's disease. None of the CBD patients had age of presentation before 45, severe autonomic dysfunction, delusions or hallucinations unrelated to levodopa or good and sustained response to levodopa.

Clinicians unfamiliar with the less common manifestations of these disorders, without a high index of suspicion, face a considerable diagnostic challenge, particularly at early stages of disease. Diagnostic markers are needed, but they will only be useful if these disorders are suspected. Improved recognition of the early stages of these disorders may lead to more

appropriate management and counseling. In addition, accurate, early diagnosis may facilitate investigations centered on the pathogenesis of these disorders and biologic therapeutic interventions to slow their progression.

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