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# Which clinical features differentiate progressive supranuclear palsy (Steele–Richardson–Olszewski syndrome) from related disorders?
## A clinicopathological study

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**Summary**
*The difficulty in differentiating progressive supranuclear palsy (PSP, also called Steele–Richardson–Olszewski syndrome) from other related disorders was the incentive for a study to determine the clinical features that best distinguish PSP. Logistic regression and classification and regression tree analysis (CART) were used to analyse data obtained at the first visit from a sample of 83 patients with a clinical history of parkinsonism or dementia confirmed neuropathologically, including PSP (*n *= 24), corticobasal degeneration (*n *= 11), Parkinson's disease (PD,* n *= 11), diffuse Lewy body disease (*n *= 14), Pick's disease (*n *= 8) and multiple system atrophy (MSA,* n *= 15). Supranuclear vertical gaze palsy, moderate or severe postural instability and falls during the first year after onset of symptoms classified the sample with 9% error using logistic regression analysis. The CART identified similar features and was also helpful in identifying particular attributes that separate PSP from each of the other disorders. Unstable gait, absence of tremor-dominant disease and absence of a response to levodopa differentiated PSP from PD. Supranuclear vertical gaze palsy, gait instability and the absence of delusions distinguished PSP from diffuse Lewy body disease. Supranuclear vertical gaze palsy and increased age at symptom-onset distinguished PSP from MSA. Gait abnormality, severe upward gaze palsy, bilateral bradykinesia and absence of alien limb syndrome separated PSP from corticobasal degeneration. Postural instability successfully classified PSP from Pick's disease. The present study may help to minimize the difficulties neurologists experience when attempting to classify these disorders at early stages.*

**Keywords**: progressive supranuclear palsy; statistical methods; diagnosis (parkinsonian disorders); classification and regression tree analysis

**Abbreviations**: CART = classification and regression tree analysis; MSA = multiple system atrophy; PSP = progressive supranuclear palsy

## Introduction

There is considerable awareness of the difficulty in diagnosing progressive supranuclear palsy (PSP, or Steele–Richardson–Olszewski Syndrome) (Tolosa *et al*., 1995; Litvan *et al*., 1996*a*). The diagnosis of PSP may be relatively straightforward when patients present with typical features, including early postural instability, supranuclear vertical gaze palsy, parkinsonism that does not benefit from levodopa therapy, pseudobulbar palsy and mild dementia, but PSP's clinical diversity is increasingly recognized (Lees, 1992; Daniel *et al*., 1995). PSP patients without ophthalmoplegia, with pure akinesia or dementia, or with a familial history of PSP have been reported (Nuwer, 1981; Dubas *et al*., 1983; Masliah *et al*., 1991; Matsuo *et al*., 1991; Mizusawa *et al*., 1993; Riley *et al*., 1994; de Yébenes *et al*., 1995). The diagnosis of PSP can also be arduous because of the topographical overlap of its lesions with those of other related parkinsonian and dementia disorders. In this regard, both false negative and false positive misdiagnosis can occur. Neuropathologically confirmed cases of cerebrovascular disease, diffuse Lewy body disease, multiple system atrophy (MSA), corticobasal degeneration, subcortical gliosis and even prion disease can be clinically misdiagnosed as PSP (false positive diagnosis) (Will *et al*., 1988; Gibb *et al*., 1989; Fearnley *et al*., 1991; De Bruin *et al*., 1992; Foster *et al*., 1992; Jellinger, 1995; Revesz *et al*., 1995). On the other hand, autopsy-confirmed cases of PSP can be misdiagnosed as Parkinson's disease, corticobasal degeneration, MSA or Alzheimer's disease (Jackson *et al*., 1983; Boller *et al*., 1989; Rajput *et al*., 1991; Hughes *et al*., 1992; Case records of the Massachusetts General Hospital, 1993; Jellinger, 1995).

Logistic regression analysis is a useful statistical technique for identifying the features that distinguish different nosological disorders. Another analytical approach, particularly when there are missing data, is to use the classification and regression tree (CART) (Breiman *et al*., 1984), a fairly new, well-established, non-parametric statistical technique, also called recursive partitioning, that classifies subjects in homogenous groups. There are some advantages of CART. First, very few assumptions are necessary for its use, thus, its broad applicability; secondly, ordinal or dichotomous (present versus absent) data can be used; thirdly, the method automatically identifies any interactions (e.g. synergistic effects among the variables analysed) (Breiman *et al*., 1984; Kwak *et al*., 1990). Moreover, other statistical techniques assume that all misclassifications are equally bad, whereas CART can separately penalize classification errors (Goldman *et al*., 1982). In neurology, CART has been used to develop a set of decision rules to predict stroke rehabilitation outcome (Falconer *et al*., 1994), to test neuropsychological function after trauma (Temkin *et al*., 1995) and to classify spatial patterns of EEG (Grajski *et al*., 1986).

To identify the variables separating PSP from other related disorders better, we employed both regression analysis and CART to study a sample of 83 patients with a history of parkinsonism or dementia whose complete clinical records at the first visit were available and who had an autopsy-confirmed diagnosis. Our aim was to identify the earliest clinical features that could distinguish PSP from other related disorders.

## Subjects and methods

Cases were selected from the research and clinical files of seven medical centres by neuropathologists; for their diagnoses they used the recently published NINDS (National Institute of Neurological Disorders and Stroke) neuropathological criteria for the diagnosis of PSP (Hauw *et al*., 1994), the reliability of which is substantial (Litvan *et al*., 1996*b*), and Kosaka's proposed neuropathological criteria for diffuse Lewy body disease (Kosaka, 1990) which is currently called dementia with Lewy bodies (Jellinger, 1996). Cases were included in the study only if the neuropathologists were at least 75% certain of the neuropathological diagnosis and only if all patients had complete neurological examinations, including oculomotor examinations. The certainty of the diagnosis was not based on any specific criteria but rather on the neuropathologists' judgment. From an original sample of 110 cases with a history of parkinsonism or dementia, 27 cases were excluded because (i) the sample had fewer than eight cases from a specific disorder, (ii) a case had more than one neurodegenerative disorder (combined disorders, except for diffuse Lewy body disease —occasionally associated with Alzheimer's disease) or had strokes in the basal ganglia or brainstem, or (iii) cases lacked a bedside mental status examination. Our sample of 83 cases consisted of 24 cases of PSP, 11 cases of corticobasal degeneration, 11 cases of Parkinson's disease, 14 cases of diffuse Lewy body disease, eight cases of Pick's disease and 15 cases of MSA. These disorders were chosen because of the difficulties they may present in their clinical differentiation from PSP. The demographic characteristics of the patients are shown in Table 1. Patients with MSA and Parkinson's disease had a significantly earlier age of onset, and patients with Parkinson's disease also survived significantly longer than patients with any other disorder ($P < 0.005$).

### *Data collection*

The case records were abstracted on standardized forms by eight of us (M.V., A.M., K.R.C., K.J., R.K.B.P., L.D., C.A.M. and I.L.); we followed strict instructions to record as missing any features that were not explicitly described in the records and to record the clinical descriptions uniformly, according to specific definitions provided. Because the data were retrospectively collected, we assumed that neurologists performed complete examinations and considered that a feature (e.g. supranuclear palsy) was absent when the examination (e.g. cranial nerves) was reported as being 'within normal limits' (e.g. of cranial nerves). The severity

**Table 1** *Demographic characteristics of the study sample*

| Disorder | *n* | Age at onset (years) | Disease duration (months) | Time to first visit (months) | Time between visits (months) | Early CVA (%) | Familial disease† |
|---|---|---|---|---|---|---|---|
| PSP | 24 | 63±2 | 79±8 | 44±9 | 27±9 | 4 (1/24) | 0 |
| CBD | 11 | 62±2 | 93±12 | 32±12 | 38±13 | 0 | 0 |
| MSA | 15 | 55±3* | 80±14 | 43±11 | 26±11 | 0 | 7 (1/14) |
| DLBD | 14 | 66±3 | 90±17 | 38±11 | 46±11 | 0 | 23 (3/13) |
| PD | 11 | 54±4* | 187±19* | 82±13 | 107±13* | 0 | 0 |
| Pick's disease | 8 | 66±4 | 83±19 | 41±15 | 34±15 | 0 | 14 (1/7) |

Values are mean±SEM. PSP = progressive supranuclear palsy; CBD = corticobasal degeneration; MSA = multiple system atrophy; DLBD = diffuse Lewy body disease; PD = Parkinson's disease. Early CVA = stroke before the first visit. *$P < 0.05$ for the difference from other disorders studied. †At least one relative with a similar disorder.

of gaze disturbance was classified as follows: 0 = normal; 1 = saccadic pursuit; 2 = moderate limitation; 3 = severe limitation. The severity of gait impairment was classified as follows: 0 = not affected; 1 = minimal (impaired but no assistance needed); 2 = mild (needs use of cane or walker); 3 = moderate (needs assistance of one or more persons); and 4 = severe (unable to walk even with assistance). For the purpose of this study, upward gaze limitation was considered abnormal when there was a restriction in pursuit or voluntary gaze, or both, of at least 50% of the normal range or when the upward supranuclear gaze palsy was rated as moderate to severe. The response to levodopa therapy was classified as: 0 = not administered; 1 = poor or none; 2 = moderate; 3 = good; 4 = excellent.

We analysed the ability of each potentially predictive variable (elements of history and physical examination available in medical records, $n = 150$) to discriminate patients with PSP from those without it. Thus, variables included in the analysis consisted of features that could characterize each disorder (e.g. resting tremor, axial more than limb rigidity, asymmetrical onset of parkinsonian features), except for ideomotor apraxia, which was difficult to characterize retrospectively. The other problematic variable was the response to levodopa therapy, because the drug was not administered at the first visit to 61% of the sample, including 52% with PSP, 9% with Parkinson's disease, 60% with MSA, 71% with diffuse Lewy body disease and 100% with Pick's disease. We constructed indicators for each disease, based on the most common features available that could characterize each disorder. The indicators for Parkinson's disease were presence of resting tremor, rigidity and bradykinesia; asymmetrical parkinsonism; response to levodopa treatment; tremor-dominant disease; levodopa-induced dyskinesia; absence of pyramidal signs; absence of Hughes *et al*. (1992) features indicative of a non-Parkinson's disease disorder (early severe dementia, early marked autonomic disturbance, supranuclear gaze palsy, alien limb syndrome and bulbar palsy) or absence of a modified Hughes *et al*. (1992) non-Parkinson's disease criteria excluding dysphagia. The indicators for diffuse Lewy body disease were delusions; hallucinations; hallucinations at onset; and language disturbances (aphasia). The indicators for corticobasal degeneration were alien hand syndrome, asymmetrical parkinsonism, limb dystonia or language disturbance. The indicators for MSA were marked hypotension, orthostatic hypotension, incontinence and cerebellar and pyramidal signs. The indicators for Pick's disease were cognitive symptoms at onset, cortical dementia, aphasia, and absence of early marked autonomic disturbance, supranuclear gaze palsy, alien limb syndrome and bulbar palsy.

## *Statistical analysis*

Both logistic regression and the CART (Breiman *et al*., 1984) methodology were used for the analyses. The particular implementation of CART is using PROC RPART, written but not currently supported by T. Therneau, for use in the software package SAS (SAS Institute Inc., SAS Campus Drive, Cary, NC, USA); commercial versions are currently available through California software and SYSTAT. The idea of CART is to examine all variables, including those that are missing, one at a time to choose the best single variable with the optimal split that divides the individuals into two groups or nodes, each of which is less impure than the original according to the Gini index (Breiman *et al*., 1984). A 'tree' is constructed in this fashion by splitting each node into two until all the terminal nodes are pure (of one group only). In the event that a variable is missing for a single individual, surrogate variables with associated splits that maximize predictive association are found and at each stage these are used instead. The complete tree is usually too detailed, and it may not perform well in classifying new cases. A statistical technique called cross-validation is used to determine which unproductive splits should be pruned from the tree. It is also used to approximate the performance of the best tree more realistically, not just its overly optimistic performance on the data used in its construction. To evaluate how well a tree will do on future data (cross-validated error), a random group of patients was selected from the data, and the group left out was used to test the tree. The realistic performance approximated using the cross-validated error for a specified loss structure (penalty for errors committed in the

**Table 2** *Comparison of statistical results*

| Diagnostic comparison | Logistic regression | CART |
|---|---|---|
| PSP versus non-PSP | Supranuclear vertical gaze palsy, falls during first year of onset, moderate-to-severe gait impairment | Supranuclear vertical gaze palsy |
| PSP versus PD | Tremor-dominant disease, unstable gait | Levodopa response |
| PSP versus MSA | Supranuclear vertical gaze palsy, age at onset | Supranuclear vertical gaze palsy |
| PSP versus DLBD | Supranuclear vertical gaze palsy, gait instability | Supranuclear vertical gaze palsy, unstable gait, delusions |
| PSP versus CBD | Early gait abnormality, unilateral onset of tremor | Gait abnormality, severe upward gaze palsy, bilateral bradykinesia, alien limb syndrome |
| PSP versus Pick's disease | Gait abnormality | Postural instability |

PSP = progressive supranuclear palsy; PD = Parkinson's disease; MSA = multiple system atrophy; DLBD = diffuse Lewy body disease; CBD = corticobasal degeneration. CART = classification and regression tree analysis.

classification) is reported for each tree. We chose to penalize false positive more than false negative errors in diagnosis. Statistical significance was defined as $P < 0.05$.

## Results

### *Progressive supranuclear palsy versus non-PSP*

For the stepwise logistic regression analysis of PSP versus non-PSP, we converted each of the missing data to the absence of a symptom because, with this technique, one missing value in a case deletes that case from the analysis. For stepwise logistic models with 0–1 loss (the default), the variables included in the model were vertical pursuit gaze (dichotomous, i.e. moderate or severe gaze palsy versus no abnormality or saccadic pursuit), downward gaze supranuclear palsy, upward gaze supranuclear palsy, gait abnormality, falls during the first year (early) or not, gait (dichotomous, i.e. moderately or severely impaired versus normal or minimally impaired and does not require assistance), postural instability, aphasia, delusions, hallucinations, marked hypotension, incontinence, all of resting tremor, rigidity and bradykinesia, pyramidal signs (Babinski) and the indicators of the other five diseases based on the other variables (*see* Data collection). Supranuclear vertical gaze palsy ($P = 0.0001$), falls during the first year after onset of symptoms ($P = 0.0001$) and moderate or severe gait impairment ($P = 0.0028$) were the significant variables identified (Table 2). The predicted values of this logistic model, using 0.5 as the cutoff, misclassified four PSP cases and four non-PSP cases (two corticobasal degeneration and two MSA), with an error rate of 9%, at the first visit (on average 3.5 years after disease onset). The logistic linear equation using vertical gaze abnormality (non-dichotomous) and early falls misclassified seven PSP cases and three non-PSP cases (error rate 12%).

We also performed a logistic regression analysis without converting the missing data to the absence of a symptom ($n = 83$) and identified supranuclear vertical gaze palsy ($P = 0.0001$; odds ratio, 103; 95% confidence interval, 17–2062) and falls during the first year after onset of symptoms ($P = 0.001$; odds ratio, 47; 95% confidence interval, 7–972). Because PSP was our outcome measure, odds ratios >1 predict PSP and those <1 predict the disorder with which PSP is being compared.

When CART was used to separate PSP cases versus non-PSP cases, the rule was a split on supranuclear vertical gaze palsy. Sixty cases (five PSP and 55 non-PSP) had normal or saccadic pursuit, and 23 cases had supranuclear vertical gaze palsy (19 PSP and four non-PSP: two corticobasal degeneration and two MSA). The actual error rate and cross-validated error was 10%.

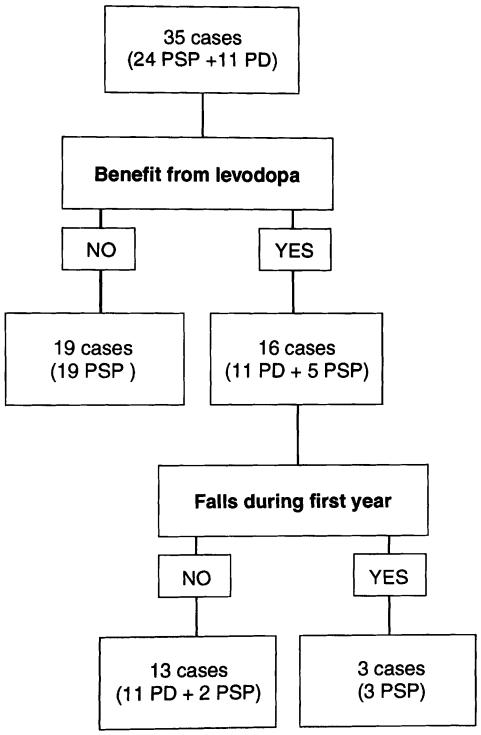


**Fig. 1** CART analysis of 24 cases of progressive supranuclear palsy (PSP) and 11 cases of Parkinson's disease (PD).

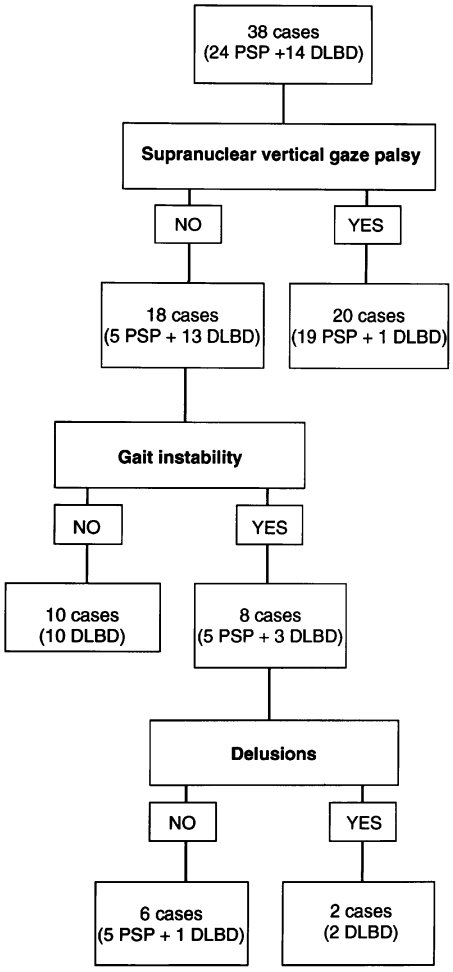


**Fig. 2** CART analysis of 24 cases of progressive supranuclear palsy (PSP) and 14 cases of diffuse Lewy body disease (DLBD).

## *Progressive supranuclear palsy versus Parkinson's disease*

The CART rule in the analysis of PSP versus Parkinson's disease was a split on levodopa response (dichotomous, i.e. none or poor versus moderate or good), with supranuclear vertical abnormality as the surrogate measure (Fig. 1). Nineteen PSP cases had a none or poor response to levodopa treatment or a supranuclear vertical gaze abnormality and 16 cases (11 PD and five PSP) had a moderate or good response to levodopa or no abnormality of vertical gaze. The 16 cases were split on falls during the first year, which identified three PSP cases. Thus, the error rate was 5% (two misdiagnosis of PSP for Parkinson's disease in 35 cases). The cross-validated error rate was 10%. A separate logistic regression analysis converting the missing levodopa data (levodopa not administered) to none or poor levodopa response yielded similar results.

The logistic regression analysis (deleting if necessary any cases with missing data) identified a model ($P = 0.0001$, $n = 34$) consisting of tremor dominant disease ($P < 0.02$; odds ratio, 0.03; 95% confidence interval, 0.001–0.4) and unstable gait ($P < 0.02$; odds ratio, 25; 95% confidence interval, 2.2–676) (Table 2).

## *Progressive supranuclear palsy versus MSA*

The CART rule in the analysis of PSP versus MSA was a split on supranuclear vertical gaze palsy. Eighteen cases (five PSP and 13 MSA) had normal eye movements and 21 cases (19 PSP and two MSA) had supranuclear vertical gaze palsy. Thus, the error rate was 18%; the cross-validated error was 23%.

The logistic regression analysis (deleting if necessary any cases with missing data) identified a model ($P = 0.0001$, $n = 39$) consisting of age at onset ($P < 0.01$, odds ratio: 0.005, 95% confidence interval: 0.0001–0.27) (earliest in MSA) and supranuclear vertical gaze palsy ($P < 0.001$; odds ratio, 40; 95% confidence interval, 5.8–660) (Table 2).

## *Progressive supranuclear palsy versus diffuse Lewy body disease*

The CART rule in the analysis of PSP versus diffuse Lewy body disease was a split on supranuclear vertical gaze palsy (Fig. 2). Twenty cases (19 PSP and one diffuse Lewy body disease) had supranuclear vertical gaze palsy. Eighteen cases (five PSP and 13 diffuse Lewy body disease) had no gaze abnormality. The 18 cases were split on gait-instability (dichotomous, i.e. unstable gait versus no abnormality). Ten cases (all diffuse Lewy body disease) had normal gait stability and eight cases (five PSP and three diffuse Lewy body disease) had abnormal gait stability. The eight cases were split on delusions. Six cases (five PSP and one diffuse Lewy body disease) did not have delusions and two cases (both diffuse Lewy body disease) had delusions. The actual error was 5% and the cross-validated error was 13%. When supranuclear palsy was disregarded the split was on gait balance. Eleven cases (10 diffuse Lewy body disease and one PSP) had normal balance and 27 cases (23 PSP and four diffuse Lewy body disease) had abnormal balance. The 27 cases were split by the presence of delusions. Three cases (all diffuse Lewy body disease) had delusions and 24 cases (23 PSP and one diffuse Lewy body disease) did not have delusions. The actual error rate was 7% and the cross-validated error was 20%.

The logistic regression analysis (deleting if necessary any cases with missing data) identified a model ($P = 0.0001$, $n = 36$) consisting of supranuclear vertical gaze palsy ($P < 0.02$; odds ratio, 19; 95% confidence interval, 1.8–598) and gait instability ($P < 0.01$; odds ratio, 34; 95% confidence interval, 3.3–1081) (Table 2).

## *Progressive supranuclear palsy versus corticobasal degeneration*

The CART rule on PSP versus corticobasal degeneration was a split on gait abnormality (Fig. 3). Eight cases (one PSP

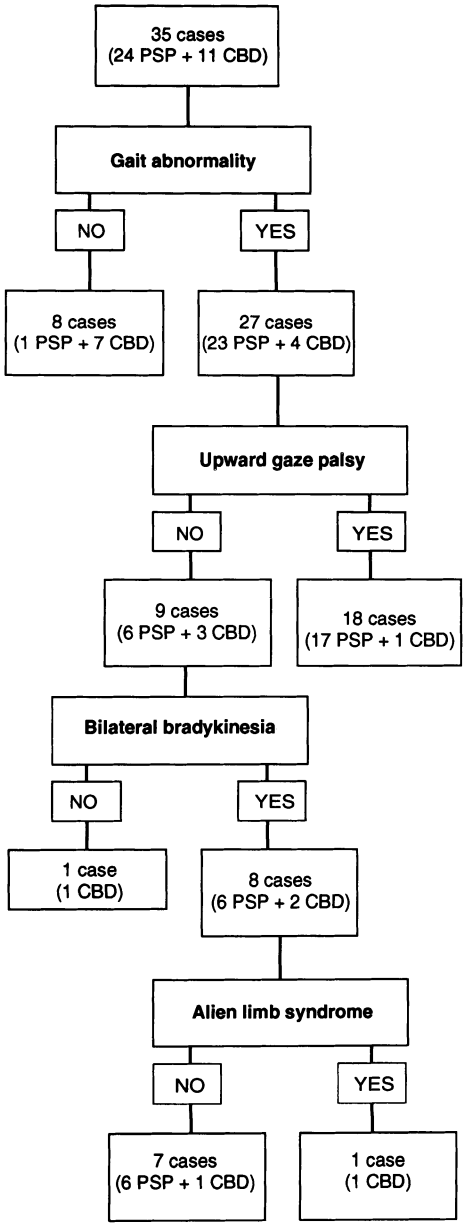


**Fig. 3** CART analysis of 24 cases of progressive supranuclear palsy (PSP) and 11 cases of corticobasal degeneration (CBD).

and seven corticobasal degeneration) had normal gait and 27 cases (23 PSP and four corticobasal degeneration) had abnormal gait. The 27 cases were split on upward gaze palsy. Eighteen cases (17 PSP and one corticobasal degeneration) had upward gaze palsy and nine cases (six PSP and three with corticobasal degeneration) did not have upward gaze palsy. The nine cases split on bilateral bradykinesia. Eight cases (six PSP and two corticobasal degeneration) had moderate to severe bilateral bradykinesia and one case (corticobasal degeneration) did not have bilateral bradykinesia. The eight cases were split on alien limb syndrome. One case (corticobasal degeneration) had alien limb syndrome and seven cases (six PSP and one corticobasal degeneration) did not have alien limb syndrome. The actual error was 9% and the cross-validated error was 27%.

The logistic regression analysis (deleting if necessary any cases with missing data) identified a model ($P = 0.0001$, $n = 31$) consisting of unilateral onset of tremor, supporting corticobasal degeneration ($P < 0.03$; odds ratio, 0.05; 95% confidence interval, 0.001–0.6) and early gait abnormality favouring PSP ($P < 0.003$; odds ratio, 78; 95% confidence interval, 6.6–3073) (Table 2).

### *Progressive supranuclear palsy versus Pick's disease*

The CART rule on PSP versus Pick's disease was a split on postural instability. Twenty-three cases (all PSP) had postural instability and nine cases (one PSP and eight Pick's disease) did not have postural instability. The actual error was 3% and the cross-validated error 0.

The logistic regression analysis (deleting if necessary any cases with missing data) identified a model ($P = 0.0005$, $n = 32$) consisting of gait abnormality ($P < 0.004$; odds ratio, 38; 95% confidence interval, 4.4–891) (Table 2).

## Discussion

In general, the different types of statistical analyses identified the same features, including supranuclear vertical gaze palsy and moderate or severe postural instability with falls during the first year after onset of symptoms, for the correct classification of PSP versus non-PSP patients (Table 2). In fact, these analyses were also the basis for the main inclusionary features proposed for its probable diagnosis by the NINDS–SPSP clinical criteria (Litvan *et al.*, 1996*c*). Supranuclear vertical gaze palsy may occur in other parkinsonian disorders such as corticobasal degeneration, diffuse Lewy body disease or, less commonly, MSA, but when associated with early balance disturbances and falls, it differentiates PSP from the most common related disorders. We also searched for more distinctive features that could help us distinguish PSP from each of the other related parkinsonian or frontal lobe-type dementia syndromes.

Parkinson's disease may be difficult to differentiate from PSP in its early stages when there are no oculomotor abnormalities. Our data showed that the absence of a response to levodopa therapy is a critical feature (with supranuclear vertical gaze palsy as a surrogate), as are early postural instability and falls (within the first year after onset of symptoms). When all these features were considered, the cross-validated error rate at the first visit was small (13%). Similarly, the logistic regression analysis identified the presence of unstable gait and absence of tremor-dominant disease. Although it was not obvious in our sample, asymmetrical onset of the parkinsonism, when present, may also facilitate the differentiation of PSP from Parkinson's disease (Quinn, 1995).

Patients with MSA may also be difficult to distinguish from PSP patients. The MSA patients had an earlier age of onset, but the duration of symptoms was similar in both disorders. Both patient groups may present with gait disturbances, broad-based gait, early dysarthria, frontal-lobe type symptomatology and pyramidal signs (Quinn and Marsden, 1993; Colosimo *et al*., 1995). Frontal lobe dysfunction in MSA, however, is not as severe as in PSP (Grafman *et al*., 1990; Robbins *et al*., 1992, 1994). Nonetheless, in our sample, the main feature that helped to differentiate PSP patients was the presence of supranuclear vertical gaze palsy. However, vertical supranuclear paresis produced considerable actual and cross-validated errors (18% and 23%). Vertical supranuclear paresis, although rare, has been reported in neuropathologically confirmed MSA (Wenning *et al*., 1995). As in previous reports (Wenning *et al*., 1995), the reduced downward gaze in our patients was mild, never severe. Moreover, at early stages the vertical supranuclear paresis of MSA patients was associated with horizontal gaze paresis, in contrast to what is found in PSP patients. In addition to supranuclear gaze palsy, the logistic regression analysis identified age at onset as a significant feature. Similar to previous reports (Wenning *et al*., 1994, 1995; Colosimo *et al*., 1995), at onset of PSP symptoms our patients were usually in their sixties while in the MSA patients were in their fifties. Other useful clinical phenomena in the differential diagnosis of PSP in prospective studies may include the quality of speech, early or severe autonomic and cerebellar features, asymmetrical onset, breathing abnormalities and polyneuropathy (except for breathing abnormalities and polyneuropathy, the other variables were included in our analysis but were not selected in the model) (Wenning *et al*., 1994, 1995). Indeed, Colosimo *et al*. (1995) examined the presenting features of 16 MSA patients from the Parkinson's Disease Brain Bank who had only parkinsonism at the end of the first 3 years and found that symptom onset was asymmetrical in 74% of them. Although urinary incontinence is not reported as a presenting symptom in PSP, our study and others (Sakakibara *et al*., 1993; Wakatsuki *et al*., 1993*b*) have found that urinary disturbances, usually urgent micturition, may be present 3 years after symptoms onset. In addition, an abnormal sphincter EMG is found fairly frequently in both disorders (Wakatsuki *et al*., 1993*a*; Pramstaller *et al*., 1995; Vallderiola *et al*., 1995).

Diffuse Lewy body disease has, on occasion, a presentation similar to that of PSP (Lewis and Gawel, 1990; Fearnley *et al*., 1991; De Bruin *et al*., 1992). Not only do both conditions have a similar age of presentation and duration of symptoms, but both may have parkinsonism with a poor response to levodopa, supranuclear vertical gaze palsy and cognitive disturbances. In our sample, supranuclear vertical gaze palsy, balance disturbances and delusions distinguished both disorders, giving a cross-validated error of 13%. Previously proposed operational criteria for the diagnosis of diffuse Lewy body disease, developed after comparing these patients with those with Alzheimer's disease (McKeith *et al*., 1992), also included psychotic features (visual and auditory hallucinations and paranoid delusions) and fluctuating cognitive impairment. In fact, these operational criteria, which also include the presence of parkinsonism or neuroleptic sensitivity syndrome, were substantially accurate in separating patients with diffuse Lewy body disease from those with Alzheimer's disease and multi-infarct dementia (McKeith *et al*., 1994). Future studies may benefit from the inclusion of neuropsychological and neuropsychiatric data (in addition to bedside examination of mental status), to improve differentiation in the cognitive and behavioural features of these disorders.

In corticobasal degeneration, the age of presentation and duration of symptoms are similar to those of PSP. Moreover, patients with corticobasal degeneration may also have symptomatology similar to that of PSP patients, including supranuclear vertical gaze palsy and postural instability, although typically of late onset (Rinne *et al*., 1994). In our sample, the presence of abnormal gait, moderate or severe supranuclear upward gaze palsy and bilateral bradykinesia distinguished PSP from corticobasal degeneration. Alien hand syndrome was a rare but helpful sign for separating cases of corticobasal degeneration. Due to the difficulties in defining ideomotor apraxia and the retrospective collection of data, we did not consider this feature in our study. In addition to gait abnormality, the logistic regression analysis identified the absence of unilateral tremor at onset as useful for differentiating PSP from corticobasal degeneration. Marked ideomotor apraxia, severe segmental dystonia, aphasia, hemi-neglect, cortical sensory deficits or myoclonus may also help classify patients with corticobasal degeneration (Gibb *et al*., 1989; Riley *et al*., 1990; Riley and Lang, 1993; Gimenez-Roldan *et al*., 1994; Rinne *et al*., 1994; Pillon *et al*., 1995).

Pick's disease shares with PSP a similar age of presentation and duration of symptoms, frontal-lobe type symptomatology and, occasionally, parkinsonism. In our sample, postural instability and gait abnormality, more than supranuclear vertical gaze palsy, were the main features that accurately differentiated these two disorders.

Even though arteriosclerotic pseudoparkinsonism could mimic many of the features of PSP, we were unable to gather more than three autopsy-confirmed cases that would mimic PSP from the seven medical centres involved in our study. In arteriosclerotic pseudoparkinsonism, the pattern of presentation (at times a stepwise course) asymmetry of signs and lower body parkinsonism may help in the clinical differentiation (Dubinsky and Jankovic, 1987; Winikates and Jankovic, 1994). Clinical reports that stroke is more commonly associated with PSP than with other parkinsonian disorders need to be confirmed (Dubinsky and Jankovic, 1987; Winikates and Jankovic, 1994). Only one of our patients had a stroke (temporal infarct) before the onset of the PSP symptoms; we did not exclude any cases with associated stroke.

Although the symptomatology of PSP patients may be similar to that found in postencephalitic parkinsonism

(supranuclear vertical gaze palsy, frontal type of behavioural disturbances, parkinsonism, gait instability), a study in which neurologists had to diagnose PSP and other related disorders (Litvan *et al*., 1996*a*) revealed that neither senior nor junior neurologists had difficulty in distinguishing between these two entities. Usually, postencephalitic parkinsonism patients have an earlier age at onset, longer duration of symptoms, oculogyric crisis, a history of encephalitis lethargica, and are very sensitive to low doses of levodopa, with both a favourable response and troublesome side-effects (Duvoisin and Yahr, 1965; Duvoisin *et al*., 1972; Calne and Lees, 1988). On the other hand, PSP and postencephalitic parkinsonism may be impossible to differentiate histologically (Geddes *et al*., 1993; Litvan *et al*., 1996). Postencephalitic parkinsonism has practically disappeared, so the question of whether postencephalitic parkinsonism has changed its phenotype and evolved into PSP or whether an earlier generation of physicians failed to differentiate these two disorders because of their similar presentation may be difficult to answer. In this regard, an interesting case of possible overlap between these two disorders was recently reported (Pramstallar *et al*, 1996), but unfortunately without neuropathological confirmation.

Occasionally, neuropathologically confirmed PSP cases are clinically confused with Alzheimer's disease (Litvan *et al*, 1996*a*). Both PSP and Alzheimer's disease have a progressive course and similar age at onset. Both disorders display varying degrees of cognitive and extrapyramidal features. However, while aphasia is usually observed in cases of Alzheimer's disease, in our series, none of the typical PSP patients presented with aphasia; the only patient with aphasia and PSP was excluded because there was concomitant Alzheimer's disease. Furthermore, although amnesia is a hallmark of Alzheimer's disease, most patients with PSP have relatively mild learning and recognition deficits ( Pillon *et al*., 1986, 1991, 1994; Litvan *et al*., 1989, 1994). Moreover, features such as supranuclear vertical gaze palsy, when present, early postural instability and falls, pyramidal signs and early onset of akineto-rigid parkinsonism and pseudobulbar palsy should help differentiate PSP from Alzheimer's disease.

With respect to methodological issues, the main problem with our retrospective data collection was when in the disease course patients first consulted a neurologist. A variety of factors in patients, disease and medical setting may differ in persons searching care early versus late in an illness. Since the death date is reliable, one could imagine recording the data by time until death. However, for retrospectively collected data, it may be difficult to determine whether the physicians recorded the initial features of the different diseases. Prospectively and uniformly collected data would be quite useful for staging each disease.

A cautionary note must be sounded concerning the clinical implications of the statistical procedures, particularly CART, because of the limited amount of data concerning these relatively rare disorders. The CART procedure works best with hundreds of cases and fewer variables. There may be some question about the robustness of any resultant complicated trees. However, even with our most complicated trees (e.g. corticobasal degeneration), our results are generally in agreement with what has been proposed in the literature (Rinne *et al*., 1994).

It is also important to note that although each disease is pathologically confirmed, the prevalence of the various diseases in the US population is not represented proportionally in this study. In fact, by design, there was an effort to oversample the PSP cases and (probably) undersample Parkinson's disease cases. This is nonetheless an important issue in the performance of the statistical procedures and in the choice of an appropriate loss structure for either a CART analysis or a (logistic) discriminant analysis. The choice of the particular loss structure plays a crucial role in the kinds of models that are identified, with both logistic regression and CART.

The fact that two quite different statistical approaches are in general agreement and concord with previous clinical studies reinforces our findings. The large sample size and case mix close to what we found in our medical practice may contribute to the relevance of our conclusions. Studies like ours may help decrease the difficulties neurologists experience when attempting to classify these disorders. The accurate clinical classification of these neurodegenerative disorders will help narrow the scope of the causes, which in turn will enable physicians to administer the appropriate therapy that could slow or halt their course.

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