Automated Differential Diagnosis of Early Parkinsonism using Metabolic Brain Networks: A Validation Study

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ABSTRACT

The differentiation of idiopathic Parkinson’s disease (IPD) from multiple system atrophy (MSA) and progressive supranuclear palsy (PSP), the most common atypical parkinsonian “look-alike” syndromes (APS), can be clinically challenging. In these disorders, diagnostic inaccuracy is more frequent early in the clinical course when signs and symptoms are mild. Diagnostic inaccuracy may be particularly relevant in trials of potential disease-modifying agents, which typically involve participants with early clinical manifestations. In an initial study (Tang et al., Lancet Neurol 2010), we developed a probabilistic algorithm to classify subjects with clinical parkinsonism but uncertain diagnosis based upon the expression of metabolic covariance patterns for IPD, MSA, and PSP. Classifications based on this algorithm agreed closely with final clinical diagnosis. Nonetheless, blinded prospective validation is required before routine use of the algorithm can be considered. Methods: We used metabolic imaging to study an independent cohort of 129 parkinsonian subjects with uncertain diagnosis; 77 (60%) had symptoms for 2 years or less at the time of imaging. After imaging, subjects were followed by a blinded movement disorders specialist for an average of 2.2 years before a final diagnosis was made. By applying the algorithm to the individual scan data, the probabilities of IPD, MSA and PSP were computed and used to classify each of the subjects. The resulting image-based classifications were then compared to the final clinical diagnosis. Results: Using the original two-level logistical classification algorithm, IPD subjects were distinguished from APS with 94% specificity and 96% positive predictive value (PPV). The algorithm achieved 90% specificity and 85% PPV for MSA, and 94% specificity and 94% PPV for PSP. Diagnostic accuracy was similarly high (specificity and PPV > 90%) for parkinsonian subjects with short symptom duration. In addition, 25 subjects were classified as Level-I Indeterminate Parkinsonism and four...
more subjects as Level-II Indeterminate APS. **Conclusion:** Automated pattern-based image classification can improve diagnostic accuracy in patients with parkinsonism, even at early disease stages.

**Keywords:** Parkinson’s disease, differential diagnosis, brain networks, glucose metabolism, automated classification algorithm
INTRODUCTION

Accurate early diagnosis of Parkinson’s disease (IPD) remains a clinical challenge. Motor signs of parkinsonism, particularly akinesia and rigidity, feature prominently in the presentation of IPD as well as atypical parkinsonian “look-alike” syndromes (APS), including multiple system atrophy (MSA) and progressive supranuclear palsy (PSP). As a result, up to 35% of patients with parkinsonism are initially misdiagnosed (1) and an even lower accuracy (53%) is found in clinical diagnosis of early IPD patients responsive to medication (2). Accurate differential diagnosis of individual subjects in this population is critical for a number of reasons. IPD and APS differ with respect to the natural history of the illness and the response to antiparkinsonian treatment (3). Misdiagnosis can, therefore, be a relevant consideration in the design of clinical trials to assess new therapies, particularly those directed at early, untreated patients (4).

A number of structural magnetic resonance imaging (MRI) techniques have been used to discriminate individuals with IPD from APS based upon differences in tissue signal and/or regional volume loss (5,6). Radionuclide imaging with positron emission tomography (PET) and single photon emission computed tomography (SPECT) in conjunction with dopaminergic tracers have also been proposed for this purpose (7,8). Differential diagnosis of parkinsonian disorders based on these methods has generally relied upon the analysis of imaging signal from single brain regions, most notably the basal ganglia. Given that the basal ganglia are involved in both IPD and APS, measurements of anatomical and/or functional change in these regions may not be specific enough for accurate differential diagnosis at the individual case level.

An alternative imaging approach for the differential diagnosis of parkinsonian movement disorders involves spatial covariance mapping, a form of pattern analysis (9-11). Neurodegenerative disorders such as IPD, MSA, and PSP are characterized by stereotyped
patterns of regional change on postmortem examination. Analogously, in living patients, these illnesses are associated with characteristic disease-related patterns of abnormal cerebral function identified in the resting state (9,12,13). Given the high reproducibility of disease-related topographies across individual subjects and populations (9,12,14,15), quantitative indices of pattern expression can be used as a functional descriptor of disease progression at the network level in individual subjects (11,16,17).

Along these lines, we explored the possibility of using subject expression value for multiple disease-related patterns in concert to categorize individual patients based upon their scans. As a proof-of-principle, we developed a logistical regression algorithm based on computed subject scores for previously validated metabolic covariance patterns for IPD (PDRP: 9,14,18,19), MSA (MSARP: 20,21), and PSP (PSPRP: 20,22) to classify a North American training cohort of 167 individuals with parkinsonism with an inconclusive clinical diagnosis. These subjects underwent metabolic brain imaging an average of 2.6 years before a final clinical diagnosis was made. The pattern-based probabilistic algorithm provided high specificity (94-97%) in discriminating IPD from APS as well as MSA from PSP. Leave-one-out cross validation was applied to these data revealing high level replicability for this diagnostic algorithm (11).

Even so, the clinical utility of this approach could not be considered further without validation in an independent testing cohort. In the current study, we applied the original logistic algorithm to metabolic scans from an Indian testing cohort of 129 parkinsonian subjects with uncertain clinical diagnosis who were followed by movement disorders experts blind to the imaging results. The primary objective of this study was to prospectively validate the original logistic classification algorithm, previously developed from the North American cohort (11), in the new Indian cohort. In addition, because the greatest clinical challenge exists in patients with relatively
recent symptom onset, subjects with relatively short disease duration (≤ 2 years) were preferentially chosen as participants and separately analyzed in this validation cohort.

MATERIALS AND METHODS

Patients

165 parkinsonian subjects with uncertain clinical diagnoses were referred for diagnostic $^{18}$F-fluorodeoxyglucose ($^{18}$F-FDG) PET between November 2008 to January 2011 (Figure 1). Of these, 36 subjects were excluded because of structural abnormalities on routine MRI (n=10: basal ganglia ischemia (n=3), hydrocephalus (n=2), and severe brain atrophy (n=5)), alternative final clinical diagnosis (n=4: dementia with Lewy bodies (n=1), normal pressure hydrocephalus (n=1), and frontotemporal dementia /progressive non-fluent aphasia (n=2)), and lack of final clinical diagnosis due to inadequate follow-up (n=22).

The remaining 129 subjects (gender: 90M/39F; age: 56.2±10.6 years [mean±SD]; motor Unified Parkinson’s Disease Rating Scale [UPDRS]: 25.1±9.4; symptom duration: 2.7±1.5 years) underwent $^{18}$F-FDG PET at the Institute of Nuclear Medicine and Allied Sciences (INMAS), New Delhi, India. Of these, 77 (60%) subjects (gender: 54M/23F; age: 56.8±9.7 years) had symptom duration of 2 years or less and comprised a short-duration subgroup that was separately analyzed. In each of the subjects, the final clinical diagnosis was made by a movement disorders specialist after at least two office visits. The mean time interval between imaging and final diagnosis was 2.2±0.4 years after imaging. In all cases, the diagnosis was based upon consensus criteria for the diagnosis of IPD (United Kingdom Brain Bank Criteria (23)), MSA (24) and PSP (25), and was confirmed by a second movement disorders specialist. Both clinical experts were blinded to the imaging findings at the time of final clinical diagnosis. Because of
the excellent diagnostic agreement between the two specialists (Kappa $\kappa=0.91$, 95% confidence interval=[0.84, 0.98]), as well as the close concordance with postmortem reported for movement disorders experts after two years of clinical follow-up (26), we chose the final clinical diagnosis as the endpoint for the current study.

The study was approved by the ethical committee at INMAS and written informed consent was obtained from each patient after a detailed explanation of the procedure.

**Imaging and Preprocessing**

$^{18}$F-FDG PET was performed on patients after a 12-hour fast. Antiparkinsonian medications were withheld for at least 12 hours before imaging. Subjects received 185-296 MBq (5-8 mCi) of $^{18}$F-FDG by intravenous injections with eyes open in a silent, dimly lit room. Scanning was performed on the Discovery STE16 PET tomograph (General Electric Medical Systems, Milwaukee, WI, USA) at INMAS. This camera has a transaxial resolution of 5.12 mm full width at half maximum (FWHM) in 3-dimensional (3D) mode at an offset of 1 cm from the center of the field of view. An initial scout film of the head was performed, followed by low dose computed tomography (CT) for attenuation correction and co-registration. PET imaging was begun 60 minutes post-injection; a single bed 3D emission scan was acquired for 20 minutes for each subject.

To ensure the compatibility in this validation study, we used the same protocols as employed in our proof-of-principle study for all procedures of image preprocessing and network computations (11). Specifically, image preprocessing was performed using statistical parametric mapping (SPM) software (Wellcome Department of Cognitive Neurology, University College, London, UK), running on Matlab (Mathworks Inc., Natick, MA). $^{18}$F-FDG PET images were
spatially normalized into a standard brain space of the International Consortium for Brain Mapping (ICBM) (27) and smoothed with a 10 mm Gaussian filter to increase the signal to noise ratio, as described previously (28).

**Network Computations**

Expression values (subject scores) for each of the three relevant previously validated disease-related metabolic covariance patterns (PDRP, MSARP, and PSPRP) were computed on a prospective individual scan basis as described elsewhere (10,13) using existing software (ScAnVp, freely available at http://www.feinsteinneuroscience.org/). Subject scores for each disease pattern were standardized (z-scored) with respect to corresponding values from the same group of 42 healthy volunteer subjects (age: 51.6±14.6 years) used for reference in the original proof-of-principle study (11). As before, subject scores for each pattern were standardized such that the mean expression value for the reference sample was zero, with a standard deviation of one.

**Differential Diagnosis**

We applied the previously developed logistic classification algorithm (11) to the PDRP, MSARP, and PSPRP subject scores from each of the participants of the Indian testing cohort. The original logistic models for classification of IPD, MSA and PSP derived from the North American training cohort (11) are described in Supplemental Table 1. Prospective application of these models allowed us to calculate the probability of each disease for individual subjects of the current cohort. Based on these probabilities, we classified each of the subjects according to a two-level procedure, as previously reported (11). At Level I, each subject was classified as IPD or APS, or as Indeterminate Parkinsonism, by comparing the subject’s probabilities to the cut-off
probabilities for IPD ($P_{IPD}=0.81$) and APS ($P_{APS}=0.79$) determined in the original study (11).

Patients who had a higher probability than the cut-off value for IPD were classified as IPD, while those with a higher probability than the cut-off value for APS were classified as APS. Subjects with probabilities lower than the cut-off values of both IPD and APS were classified as Indeterminate Parkinsonism. At Level II, subjects classified at Level I as APS were further subclassified as MSA or PSP, or as Indeterminate APS, using the previously reported cut-off probabilities for MSA ($P_{MSA}=0.74$) and PSP ($P_{PSP}=0.55$) (11). Likewise, subjects with a higher probability than cut-off for either of the two major APS subtypes were classified as MSA or PSP. Subjects with probabilities lower than the cut-off values for the two conditions were classified as Indeterminate APS.

Image-based classification was performed in each subject without knowledge of the final clinical diagnosis. Based on the classification results of individual subjects, discriminative measures (sensitivity, specificity, positive predictive value [PPV], and negative predictive value [NPV]) for the analysis at each level (Level I: PD and APS; Level II: MSA and PSP) were computed separately for the whole group ($n=129$) and for the short duration sample ($n=77$). At each level, Indeterminate cases were included as misclassified subjects in the calculation of discriminative measures. Because Level-I Indeterminate cases had a similar likelihood (approximately 50%) of having IPD or APS, these subjects were not further classified as MSA or PSP at Level II (11). Thus, as implemented in the original logistic algorithm, Level-I Indeterminate cases in the present cohort were excluded from the Level II analysis as well as the calculation of discriminative measures at this level. Moreover, because the proportion of APS patients in this Indian cohort (37%) was substantially higher than the expected prevalence in the general population (29), the PPVs reported in this study were features of the current sample,
which was representative of the patients in the referring tertiary movement disorders clinics. In addition, receiver-operating characteristic (ROC) analysis was conducted for each disease condition using the entire dataset and was then limited to the subgroup of short-duration (≤ 2 years) cases.

Logistic regression analysis was performed in SAS 9.3 (SAS Institute Inc., Cary, NC) and other statistical tests were performed in SPSS 14.0 (SPSS Inc., Chicago, IL). All tests were considered significant for p<0.05.

RESULTS

Analysis of the Whole Group

The demographic features of the subjects are summarized in Table 1. Among the 129 subjects with uncertain parkinsonism that were included, 81 were subsequently diagnosed clinically as having IPD and all of them were responsive to levodopa treatment. Of the remaining subjects, 20 were diagnosed with MSA and 28 with PSP. The average disease duration was 2.7±1.5 years at the time of imaging; a final diagnosis was made an average of 2.2±0.4 years following the imaging procedure.

PDRP, MSARP, and PSPRP expression values for the subjects, grouped by final clinical diagnosis, are displayed in Figure 2. The resulting subject scores were used in conjunction with the previously reported logistic algorithm to compute the probabilities of IPD and APS in each of the subjects. We then compared the image-based classification with their final clinical diagnosis. Of the 129 patients, 70 (67 were diagnosed clinically as IPD, 1 as MSA and 2 as PSP) were classified as having IPD, while 34 (4 were subsequently diagnosed clinically as IPD, 14 as MSA and 16 as PSP) were classified as having APS. The remaining 25 subjects (10 IPD, 5 MSA and...
10 PSP), accounting for 19% of the total, did not satisfy the pre-specified cutpoint criteria for classification as either IPD or APS (Figure 3A, left), and were therefore categorized as Indeterminate Parkinsonism. Overall, the first-level analysis (Table 2) resulted in 83% sensitivity, 94% specificity, 96% PPV and 76% NPV for the classification of IPD, and 63% sensitivity, 95% specificity, 88% PPV and 81% NPV for the classification of APS (Table 2). The area-under-the-curve (AUC) for the ROC analyses of the whole sample (Figure 3A, right) was 0.95 (p<0.0001) for both IPD and APS.

The 34 subjects classified as APS at Level I underwent second-level analysis (Figure 3B, C, left) to further differentiate between MSA and PSP. This analysis (Table 2) resulted in 79% sensitivity, 90% specificity, 85% PPV and 86% NPV for the classification of MSA, and 100% sensitivity, 94% specificity, 94% PPV and 100% NPV for the classification of PSP. ROC analysis (Figure 3B, C, right) revealed a significant AUC of 0.93 for MSA (p<0.0001) and 0.99 for PSP (p<0.0001). In addition, four (12%; 1 IPD and 3 MSA) of the 34 subjects did not satisfy the pre-specified classification criteria for either MSA or PSP and were categorized as Indeterminate APS at the second level.

**Analysis of the Short Duration Subgroup**

77 subjects (40 IPD, 16 MSA and 21 PSP), accounting for 60% of the total, had symptoms of short duration (≤ 2 years). For this subgroup, the average duration of symptoms at the time of imaging was 1.7±0.4 years. The final clinical diagnosis in these subjects was made 2.2±0.5 years after imaging. Based on the classification algorithm, 38 of these early stage subjects were categorized as IPD (36 were subsequently diagnosed clinically as IPD, 1 as MSA and 1 as PSP), while 24 were classified as APS (1 clinically diagnosed as IPD, 11 as MSA and 12 as PSP). The
remaining 15 (19%) subjects (3 subsequently classified clinically as IPD, 4 as MSA and 8 as PSP) were categorized by the algorithm (Figure 4A, left) as Indeterminate Parkinsonism. Thus, for this early subgroup, the first-level analysis (Table 2) resulted in 90% sensitivity, 95% specificity, 95% PPV and 90% NPV for IPD, and 62% sensitivity, 98% specificity, 96% PPV and 74% NPV for APS. ROC analysis (Figure 4A, right) revealed AUC=0.96 (p<0.0001) for both IPD and APS at the first level.

Second-level analysis for the 24 subjects (Figure 4B, C, left) who were classified as APS (Table 2) resulted in 73% sensitivity, 92% specificity, 89% PPV and 80% NPV for MSA, and 100% sensitivity, 100% specificity, 100% PPV and 100% NPV for PSP. ROC analysis (Figure 4B, C, right) showed AUC=0.94 (p<0.0001) for MSA and AUC=1.00 for PSP (p<0.0001) at the second level. Three (13%; 3 MSA) of the 24 subjects were categorized as Indeterminate APS.

**Analysis of the Cases with Atrophy**

To examine potential confounding effect of brain atrophy on the classification of individual subjects, we additionally applied the algorithm to PET data from the five subjects who were excluded from the primary analysis because of atrophy. These individuals were all subsequently diagnosed with APS on clinical grounds: two with MSA and three with PSP. Of those with MSA, one subject was classified by the algorithm as Indeterminate Parkinsonism at Level I and the other as Indeterminate APS at Level II. Of the PSP cases, all were classified as Level-I Indeterminate Parkinsonism.

**DISCUSSION**

In this study, we used the original network-based logistic algorithm (11) to classify individuals in
an independent testing sample based on their metabolic scans. In accordance with the earlier findings (11), this automated image classification approach resulted in accurate differential diagnosis, with excellent discrimination of IPD from APS (Level I), and MSA from PSP (Level II) at the individual subject level. The data overall demonstrate the potential utilities of the algorithm in improving the recruitment of participants for clinical trials, as well as assisting clinicians to make more accurate diagnosis for patients with early-stage disease.

Specifically, we applied the published classification algorithm to scan data from the Indian population using the identical disease-related covariance patterns and the criteria for probabilistic classification that were employed in the previously published North American training cohort (11). Single case classification according to this approach resulted in comparably high diagnostic accuracy for IPD in the two populations (Training: 97% specificity, 98% PPV; Testing: 94% specificity, 96% PPV). Likewise, image-based classification of APS was also diagnostically accurate in both the North American and Indian samples (Training: 98% specificity, 97% PPV; Testing: 95% specificity, 88% PPV). In addition, there was no significant difference in the percentage of indeterminate cases in the Indian and the North American samples at the two levels of classification analyses (Level I: 19% vs. 14%, p=0.25; Level II: 12% vs. 12%, p=0.99; $\chi^2$ tests). In both samples, we have found that at final diagnosis, Indeterminate cases have similar likelihoods of approximately 50% of being classified clinically as IPD or APS (Level I), and MSA or PSP (Level II) (11). Thus, Indeterminate cases may represent the clinically more challenging patients who can benefit greatly from continued clinical follow-up and repeat imaging as the underlying disease progresses. Moreover, such cases, if identified, may be excluded from recruitment to help improve the efficiency and reduce the cost of clinical trials.
An important feature of the current study was the greater percentage of subjects in the Indian testing cohort with short (≤ 2 years) symptom duration compared to the original North American training sample (77/129=60% vs. 55/167=33%, respectively). Indeed, for the whole group, symptom duration at the time of imaging was substantially shorter for the current testing sample relative to the original training data set (New Delhi: 2.7±1.5 years; Manhasset: 5.0±3.8 years, p<0.0001; Student’s t-test). We note that the specificity and PPV for pattern-based classification of individual subjects at Level I (IPD vs. APS) was high (≥ 95%) even for the short duration cases (with ≤ 2 years of symptoms). Thus, the imaging-based classifications accorded well with the clinical “gold standard” diagnosis reached independently by the expert clinicians approximately 2 years after the imaging procedure. Interestingly, sensitivity at Level I was higher for IPD than for APS (90% vs. 62%), suggesting a greater rate of false negatives for classifying APS patients with short symptom duration. We note that, among the 15 short duration subjects (19%) categorized as Indeterminate Parkinsonism at Level I, 12 were later clinically diagnosed as MSA or PSP and were the majority of the false negatives for APS, resulting in a lower sensitivity. Therefore, while a subject with Indeterminate Parkinsonism (Level I) drawn at random from the whole sample has similar odds of developing APS or IPD, a comparable subject with short disease duration is four times more likely to develop APS as opposed to IPD. Level II analysis of the early APS subjects revealed that the specificity and PPV were high for both MSA (92% and 89%, respectively) and PSP (100% and 100%, respectively), and the sensitivity of MSA and PSP (73% and 100%) was higher than that reported (< 60%) for the initial clinical diagnosis of each of these conditions (30,31). Moreover, the percentage of indeterminate cases at both Level I and Level II were similar for Indian and North American short duration cases (Level
I: 19% vs. 20%, p=0.94; Level II: 13% vs. 11%, p=0.84; \( \chi^2 \) tests). Overall, these results substantiate the findings of the early patients in the original training sample (11).

The presence of substantial volume loss in early parkinsonism is suggestive of an atypical syndrome (32,33). To mitigate this potential confound, evidence of atrophy on structural imaging was adopted as an exclusion criterion in our study. In addition to confirming the accuracy of the classification algorithm in parkinsonian patients with minimal or no atrophy (11), the current findings provide information on the impact of severe volume loss on pattern-based categorization. We found that all five APS patients with severe atrophy at the time of imaging were categorized as Indeterminate by the PET-based logistical algorithm. This degree of volume loss was encountered in fewer than 3% of the referred cases. That said, the inclusion of such subjects may lead to systematic underestimation of the accuracy of this approach. It is not currently known whether diagnostic specificity can be enhanced appreciably by combining MRI volume loss measurements with metabolic pattern analysis.

We additionally note that MSA and PSP account for the majority (> 90%) of patients with atypical forms of progressive parkinsonism referred to movement disorders specialty clinics (26,34). Nonetheless, the APS category also includes corticobasal degeneration (CBD). This disorder is less common than the other APS subtypes, with an incidence of 0.6-0.9/100,000, as compared to 3.0/100,000 and 5.3/100,000 for MSA and PSP, respectively (35,36). In a recent study, we used spatial covariance mapping to identify and validate a unique CBD-related metabolic covariance pattern, termed CBDRP (22). Moreover, prospectively computed expression values for this pattern in conjunction with PSPRP accurately discriminated CBD from PSP in clinically uncertain cases (22). The goal of the present study was to validate the previously reported logistic algorithm for the same diagnostic categories used in its original
formulation (11). For that reason, we limited the current APS analysis to MSARP and PSPRP, the two disease-related patterns that were used originally to differentiate among the most common progressive forms of parkinsonism. Additional studies will be needed to determine the added value of CBDRP subject scores in discriminating IPD from APS at Level I, and in differentiating CBD from the other forms of APS at Level II.

DISCLOSURE
D.E. serves on the scientific advisory board and has received honoraria from the Michael J. Fox Foundation for Parkinson’s Research; is listed as coinventor of patents re: Markers for use in screening patients for nervous system dysfunction and a method and apparatus for using same, without financial gain; and has received research support from the NIH (NINDS, NIDCD, NIAID) and the Dana Foundation. All other authors declare no potential conflicts of interest.

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REFERENCES


FIGURE 1. Study Design and Pattern-based Classification Procedure
FIGURE 2. Three-Dimensional Plot of Pattern Expression

Expression values for the PDRP (x-axis), MSARP (y-axis) and PSPRP (z-axis) topographies (see text) are shown for the Indian validation cohort. This group was comprised of 129 parkinsonian patients with an uncertain clinical diagnosis. Based on serial clinical examinations by a movement disorders specialist blind to the scan data, 81 of these subjects were subsequently diagnosed with IPD (green circles), 20 with MSA (red triangles) and 28 with PSP (blue squares). [Pattern expression values were computed in $^{18}$F-FDG PET scans from these subjects acquired 2.2±0.4 (mean±SD) years before a final clinical diagnosis.]
FIGURE 3. Predicted Disease Probabilities for Differential Diagnosis of Patients with Uncertain Parkinsonism: Whole Sample

A. Left, Frequency distribution of the predicted probabilities for IPD (P_{IPD}, top row of x-axis) and APS (P_{APS}, bottom row of x-axis) for the current parkinsonian patient sample (n=129). This group was comprised of 81 subjects who were diagnosed clinically with IPD (yellow bars) and 48 subjects who were diagnosed with APS (green bars). Right and left dashed lines, respectively, denote the cut-off probabilities for IPD (P_{IPD}=0.81) and APS (P_{APS}=0.79) determined in our previous study (11). Subjects falling between the two dashed lines were categorized as Indeterminate. Right, Display of the receiver-operating-characteristic (ROC) curves for IPD (red) and APS (black). The area-under-the-curve (AUC) was high (≥ 0.95, p<0.0001), denoting excellent diagnostic accuracy for the two conditions based upon the logistic discrimination function indentified in the North American training set (11).

B., C. Left, Frequency distributions of the predicted probabilities for MSA (P_{MSA}, x-axis in B) and PSP (P_{PSP}, x-axis in C) in the 34 subjects who were classified as APS in the first-level analysis (see text). This group included 14 patients clinically diagnosed as having MSA (pink bars), 16 with PSP (blue bars), and 4 with IPD (orange bars). Right, ROC curves for (B) MSA (AUC=0.93, p<0.0001) and (C) PSP (AUC=0.99, p<0.0001) were consistent with excellent diagnostic accuracy for the two atypical parkinsonian variant conditions based upon the original logistic discrimination function (11).
A. APS Indeterminate IPD

Number of patients

\[ P_{\text{APS}} \]

(1.0) (0.9) (0.8) (0.7) (0.6) (0.5) (0.4) (0.3) (0.2) (0.1) (0.0)

B. Non-MSA MSA

Number of patients

\[ P_{\text{MSA}} \]

(0.0) (0.1) (0.2) (0.3) (0.4) (0.5) (0.6) (0.7) (0.8) (0.9) (1.0)

C. Non-PSP PSP

Number of patients

\[ P_{\text{PSP}} \]

(0.0) (0.1) (0.2) (0.3) (0.4) (0.5) (0.6) (0.7) (0.8) (0.9) (1.0)
FIGURE 4. Predicted Disease Probabilities for Differential Diagnosis of Patients with Uncertain Parkinsonism: Subset of Early Patients

Frequency distribution of the predicted probabilities for IPD vs. (A) APS, (B) MSA, and (C) PSP in the 77 members of the Indian patient sample (40 IPD, 16 MSA, 21 PSP) with symptoms of short duration (\( \leq 2 \) years) at the time of imaging. ROC analysis (IPD and APS: AUC=0.96, p<0.0001; MSA: AUC=0.94, p<0.0001; PSP: AUC=1.00, p<0.0001) disclosed excellent diagnostic accuracy based upon the logistical discriminant functions identified in the original training set (II).
TABLE 1. Demographic Characteristic

Values are shown as mean (SD).

*Denotes differences (p<0.05) across the three disease groups by one-way ANOVA.

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=129)</th>
<th>Symptom duration (years) ≤ 2 (n=77)</th>
<th>&gt; 2 (n=52)</th>
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<tr>
<td>Number of patients</td>
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<td>41</td>
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<td>31, 9</td>
<td>28, 13</td>
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<td>Age at FDG PET (years)</td>
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<td>53.7 (9.9)*</td>
<td>53.4 (11.7)</td>
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<tr>
<td>Symptom duration at FDG PET (years)</td>
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<td>4.2 (1.6)</td>
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<td>Hoehn and Yahr stage</td>
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<td>UPDRS</td>
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<td>19.5 (7.1)*</td>
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<td>Clinical follow-up (years)</td>
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</tbody>
</table>

| **Multiple system atrophy** |                      |                                     |            |
| Number of patients        | 20                   | 16                                  | 4          |
| Sex (male, female)        | 15, 5                | 11, 5                               | 4, 0       |
| Age at FDG PET (years)    | 58.0 (9.4)           | 57.4 (8.8)                          | 60.5 (12.5) |
| Symptom duration at FDG PET (years) | 2.2 (0.8) | 1.8 (0.3)                           | 3.5 (0.6)  |
| Hoehn and Yahr stage      | 2.7 (0.6)            | 2.6 (0.5)                           | 3.1 (0.6)  |
| UPDRS                     | 24.9 (6.7)           | 23.6 (5.5)                          | 30.3 (9.5) |
| Clinical follow-up (years) | 1.9 (0.1) | 2.0 (0.1)                           | 1.8 (0.2)  |

| **Progressive supranuclear palsy** |                      |                                     |            |
| Number of patients        | 28                   | 21                                  | 7          |
| Sex (male, female)        | 16, 12               | 12, 9                               | 4, 3       |
| Age at FDG PET (years)    | 62.5 (7.6)           | 62.2 (7.8)                          | 63.6 (7.3) |
| Symptom duration at FDG PET (years) | 2.3 (1.1) | 1.8 (0.4)                           | 3.9 (1.1)  |
| Hoehn and Yahr stage      | 2.8 (0.6)            | 2.6 (0.6)                           | 3.1 (0.4)  |
| UPDRS                     | 29.3 (5.8)           | 27.8 (5.7)                          | 33.7 (3.7) |
| Clinical follow-up (years) | 2.0 (0.2) | 2.0 (0.1)                           | 2.1 (0.4)  |

UPDRS = Unified Parkinson’s Disease Rating Scale.
TABLE 2. Discriminative Measures: Pattern-based Classification vs. Final Clinical Diagnosis

<table>
<thead>
<tr>
<th></th>
<th>All patients (n=129)</th>
<th>Symptom duration (years)</th>
<th>( \leq 2 ) (n=77)</th>
<th>( &gt; 2 ) (n=52)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Idiopathic Parkinson’s disease</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>83% (67/81)</td>
<td>90% (36/40)</td>
<td>76% (31/41)</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>94% (45/48)</td>
<td>95% (35/37)</td>
<td>91% (10/11)</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>96% (67/70)</td>
<td>95% (36/38)</td>
<td>97% (31/32)</td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>76% (45/59)</td>
<td>90% (35/39)</td>
<td>50% (10/20)</td>
<td></td>
</tr>
<tr>
<td><strong>Atypical parkinsonian syndrome</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>63% (30/48)</td>
<td>62% (23/37)</td>
<td>64% (7/11)</td>
<td></td>
</tr>
<tr>
<td>Specificity</td>
<td>95% (77/81)</td>
<td>98% (39/40)</td>
<td>93% (38/41)</td>
<td></td>
</tr>
<tr>
<td>PPV</td>
<td>88% (30/34)</td>
<td>96% (23/24)</td>
<td>70% (7/10)</td>
<td></td>
</tr>
<tr>
<td>NPV</td>
<td>81% (77/95)</td>
<td>74% (39/53)</td>
<td>91% (38/42)</td>
<td></td>
</tr>
<tr>
<td><strong>Multiple system atrophy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>79% (11/14)</td>
<td>73% (8/11)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Specificity</td>
<td>90% (18/20)</td>
<td>92% (12/13)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>PPV</td>
<td>85% (11/13)</td>
<td>89% (8/9)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>NPV</td>
<td>86% (18/21)</td>
<td>80% (12/15)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td><strong>Progressive supranuclear palsy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sensitivity</td>
<td>100% (16/16)</td>
<td>100% (12/12)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>Specificity</td>
<td>94% (17/18)</td>
<td>100% (12/12)</td>
<td></td>
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</tr>
<tr>
<td>PPV</td>
<td>94% (16/17)</td>
<td>100% (12/12)</td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>NPV</td>
<td>100% (17/17)</td>
<td>100% (12/12)</td>
<td></td>
<td>-</td>
</tr>
</tbody>
</table>

Data are shown as % (number of subjects).

PPV = positive predictive value; NPV = negative predictive value.