RESEARCH ARTICLE

Prediction of Cognitive Worsening in De Novo Parkinson's Disease: Clinical Use of Biomarkers

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ABSTRACT: Background: Cognitive impairment is a frequent and disabling feature of Parkinson's disease. Identifying the factors able to predict cognitive worsening since the early stage may improve disease management. The objective of this study was to define the best predictors of future cognitive worsening in a group of patients with newly diagnosed PD and to propose cutoff values potentially useful at the individual level.

Methods: Fifty-four consecutive drug-naive patients with de novo PD were prospectively evaluated by clinical and neuropsychological assessment, resting EEG, and ^{123}I-FP-CIT-SPECT and clinically classified into mainly motor, diffuse/malignant, and intermediate PD subtypes; they were then followed up for an average of 5 years. Cognitive outcome was defined by identifying cognitively stable or worsened patients.

Results: Step-wise logistic regression selected the posterior qEEG mean frequency and ^{123}I-FP-CIT-SPECT uptake at caudate level ($P < 0.0001$). The posterior qEEG mean frequency (cut point, 8.3 Hz) and the caudate ^{123}I-FP-CIT-SPECT uptake (cut point, 2.3, specific to nondisplaceable binding ratio) achieved 82% and 80% of accuracy, respectively, in predicting cognitive outcome. Survival analysis showed decreasing expected time to cognitive worsening associated with scores below the established thresholds for qEEG and ^{123}I-FP-CIT-SPECT and with the presence of a malignant clinical phenotype.

Conclusions: Resting EEG and ^{123}I-FP-CIT-SPECT are good predictors of future cognitive worsening, in de novo drug-naive PD patients. Wherever available, these biomarkers could add valuable prognostic information to classification into different clinical phenotypes. © 2017 International Parkinson and Movement Disorder Society

Key Words: Parkinson's disease; EEG; ^{123}I-FP-CIT-SPECT; cognition; dementia

Patients with Parkinson's disease (PD) show a wide range of nonmotor symptoms,[1] and cognitive impairment is one of the most common and disabling.[2] Almost all PD patients eventually exhibit cognitive dysfunction, and up to 80% further develop dementia.[3] Whereas several risk factors for dementia have been identified,[4-9] few studies investigated the risk factors for cognitive decline over time, including imaging biomarker findings.[2]

Actually, not only dementia but also substantial cognitive worsening should be considered as a meaningful cognitive outcome because the instrumental activities of daily living (IADLs) can be impaired to some extent in PD patients with mild cognitive impairment (MCI),[10] and health-related costs are significantly increased.[11]

Most studies investigating risk factors for subsequent cognitive decline evaluated patients at different stages of the disease and during dopaminergic treatment.[2] Instead, evaluating such factors at disease onset is unbiased from dopaminergic treatment and by the effects of a longer disease duration. Other cohort

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studies have investigated several predictors of cognitive worsening in incident PD patients, including clinical, neuropsychological, and ^{18}F-fluorodeoxyglucose PET data.[12-14] However, the risk factors need to be compared with each other to estimate their relative predictive value. Finally, it is somewhat difficult to translate group data into clinical practice if findings suitable for individual prognosis are not provided.

This prospective study aimed to evaluate baseline clinical, neuropsychological, resting quantitative electroencephalography (qEEG), and dopamine transporter (DAT) single-photon emission computed tomography (SPECT) data to define the best predictors of future cognitive worsening in a group of consecutive de novo drug-naive PD patients and to give cut points to be used in single subjects.

Methods

Subjects

Sixty-one consecutive drug-naive outpatients with de novo PD diagnosed according to current criteria[15] were prospectively evaluated. Patients were at their first assessment in a university hospital-based movement disorder unit. They underwent brain magnetic resonance imaging (MRI) or computed tomography when MRI was unfeasible to rule out other brain diseases.

The patients underwent baseline clinical evaluation, including (1) motor severity by the Unified Parkinson's Disease Rating Scale, motor section (UPDRS-III) and the Hoehn and Yahr (H&Y) scale; (2) clinical interview and questionnaires for ADLs[16] and IADLs[17] to exclude dementia; (3) the Mini-Mental State Examination (MMSE)[18]; (4) the 15-item geriatric depression scale[19] to rate depressive symptom; (5) automatic blood pressure measurements in both the supine position and after 3 minutes of standing (orthostatic hypotension [OH] was defined as a systolic blood pressure drop $\geq$ 20 mm Hg and/or a diastolic blood pressure drop $\geq$ 10 mm Hg during standing after 3 minutes[20]); (6) investigation of the presence/absence of constipation with the clinical interview; and 7) the Mayo sleep questionnaire[21] and a semistructured clinical interview[22] by a sleep medicine expert to investigate the presence/absence of probable RBD. Five patients without bed partners were excluded from the study.

The study protocol met the approval of the local Ethics Committee, and all participants signed an informed consent form in compliance with the Helsinki Declaration of 1975.

Neuropsychological Evaluation

The following neuropsychological evaluation was performed at baseline and every following year: (1) categorical and phonological verbal fluency to assess language; (2) Trail-Making Test (TMT) A, Stroop color-word test, and digit span (forward) to assess attention and working memory; (3) TMT B, Stroop color test, and symbol-digit for executive functions; (4) figure copying of the mental deterioration battery (simple copy and copy with guiding landmarks) and Clock Completion test to assess visuospatial abilities; (5) Rey Auditory Verbal Memory Test (immediate and delayed recall) and Corsi's block design to investigate memory. References for tests and normative values are listed in a previous article.[23] The presence of MCI was evaluated according to current criteria, by level 2 assessment.[24]

Baseline PD Subtype Identification

We followed the concept derived from the recent identification of PD subtypes, as proposed by Fereshtehnejad et al,[25] which pointed to the role of MCI, RBD, and OH as the strongest predictors of a malignant PD phenotype, carrying a poorer prognosis. We defined PD patients with MCI and with RBD and/or OH as belonging to the "diffuse/malignant" phenotype. In contrast, patients without MCI, RBD, and OH were labeled as the "mainly motor" phenotype. The remaining patients (ie, those with only MCI and those with RBD and/or OH) were allocated to the "intermediate" phenotype. This PD subtype identification was found to be a better solution to predicting poor prognosis compared with previously published methods.[25]

^{123}I-Ioflupane SPECT

Within 2 months since the baseline assessment, nigrostriatal dopaminergic functioning was evaluated by ^{123}I-ioflupane SPECT (^{123}I-FP-CIT-SPECT) according to the European Association of Nuclear Medicine guidelines.[26] Specific to nondisplaceable binding ratios (SBRs) at putamen and caudate levels were computed[27] and transformed into z scores, adjusted for age, based on the European normative database of 122 healthy subjects,[28] as detailed in a previous article.[29] Briefly, ^{123}I-FP-CIT images were exported in analyze format and processed by the automatic Bas-Gan algorithm[27] based on a high-definition 3-dimensional striatal template derived from the Talairach atlas, using occipital lobes uptake as the background reference region. To highlight findings in the more affected hemisphere (MAH), it was defined as the one contralateral to the more affected side of the body. In 36 patients the MAH was the left one; thus, ^{123}I-FP-CIT-SPECT images were flipped in the remaining patients. ^{123}I-FP-CIT-SPECT was available in 48 patients, whereas in 8 patients nigrostriatal impairment was documented through ^{18}F-fluoro-dopa positron emission tomography. Thus, those 8 patients were included in the clinical and qEEG analyses only.

EEG Recording and Data Processing

Within 1 month since the baseline assessment, a scalp EEG was recorded during relaxed wakefulness. qEEG relative band power for each conventional frequency band (ie, delta, theta, alpha, sigma, and beta) was calculated as a percentage of total qEEG power from the mean spectra in posterior (P3, Pz, P4, T5, T6, O1, and O2) and anterior (F3, Fz, F4, F7, and F8) cortical regions (according to the standard 10-20 electrode positions). In the same regions, the mean frequency (MF) value in the 2- to 16-Hz band was also computed. Moreover, the posterior peak frequency (PPF) was defined as the peak frequency in the power spectra of posterior cortical regions (see Supplemental eMethods for details).

Follow-Up Assessment

The 56 patients underwent 6-month-based clinical follow-up after the baseline assessment and were treated with dopamine agonists and/or L-dopa. A follow-up of at least 1 year was requested to confirm the PD diagnosis. In 2 instances a diagnosis of atypical parkinsonian syndrome was made during the follow-up. The last available follow-up visit was considered for the aim of this study (follow-up time ranging from 2 to 9 years; mean, 4.8 $\pm$ 2.2 years). The levodopa-equivalent dose (LED)[30] was computed at the last follow-up visit.

Both at baseline and at the last follow-up visit, patients were defined as cognitively normal or as affected by MCI or PD dementia (PDD), according to neuropsychological evaluation and Litvan et al criteria.[24] We then defined a 2-level cognitive outcome. Patients were considered cognitively stable (CogStable) if the baseline neuropsychological classification was maintained at follow-up, including cognitively normal patients and patients with MCI both at baseline and at follow-up visits. By contrast, patients were considered cognitively worsened (CogWorsened) if their baseline cognitive condition had deteriorated at follow-up, including cognitively normal patients at baseline who developed MCI or dementia and MCI patients who developed dementia.

Statistical Analysis

As a first descriptive step, clinical, ^{123}I-FP-CIT-SPECT and qEEG data were compared between the 3 baseline PD subtypes (ie, mainly motor, intermediate, and diffuse/malignant) by univariate analysis of variance (continuous measures) and the chi-square test (categorical measures). The relationship between the baseline PD subtype classification (3 levels) and the cognitive outcome at follow-up (2 levels) was investigated using the chi-square test to verify the ability of the clinical baseline classification in predicting cognitive outcome.

Subsequently, we compared baseline clinical, neuropsychological, ^{123}I-FP-CIT-SPECT, and qEEG data between CogStable and CogWorsened subgroups (unpaired t test for continuous measures and chi-square test for categorical measures). We applied step-wise logistic regression to evaluate the baseline features able to predict cognitive outcome. Considering the relatively small sample size for logistic regression, based on preliminary comparisons, we considered few variables for each type: they were included in the model by a forward step-wise selection. Then we applied linear discriminant analysis to compute the receiver operating characteristic (ROC) curves and to measure sensitivity and specificity of the baseline predictors of cognitive outcome. The optimal cutoff values of each predictor were defined by Youden's method.[31] The area under the ROC curve, as estimated from different metrics, was compared by evaluating the z value for paired scores according to Hanley and McNeil's formula.[32] The ability of selected predictors to distinguish those patients developing dementia among the cognitively worsened patients was then examined by discriminant analysis.

Finally, survival analysis by Kaplan-Meier estimator was applied to investigate the predictive power of the most significant parameters with respect to the time to cognitive worsening. Survival time was evaluated as the time elapsed from baseline evaluation to the shift (if any) in the cognitive state, as estimated during the visit when MCI or dementia were established and provided that the shift was confirmed at the very last visit. Censoring time was set at the time of last assessment, whereas no patients were lost to follow-up during the study. Survival curves were compared by log-rank test.

The normality assumption for analysis of variance was checked by applying the Lilliefors test to the residuals. A $P < 0.05$ was considered statistically significant. Statistical analyses were performed using Stata software (StataCorp. 2013, Stata Statistical Software: Release 13; StataCorp LP, College Station, TX) and MATLAB R2015B (The MathWorks, Inc., Natick, MA).

Results

Comparisons Among the 3 Clinical Subtypes at Baseline and Evaluation of Their Prognostic Power

Main demographic, clinical, ^{123}I-FP-CIT-SPECT, and qEEG data of the PD clinical subtypes are summarized in Table 1. As expected, the clinical features used for subtype classification (presence of RBD, OH, and MCI) were significantly different among the PD

TABLE 1. Main demographic, clinical, ^{123}I-FP-CIT-SPECT, and EEG data in the 3 PD Subtypes at baseline

PD subtypes	A: Mainly motor	B: Intermediate	C: Diffuse/malignant	*P*	Post hoc comparison[a]
Baseline					
n	19	28	7		
Age (y)	67.26 ± 8.5	68.25 ± 6.8	73.4 ± 4.4	ns	
Education (y)	12.68 ± 4.5	10.07 ± 4.0	12.57 ± 4.1	ns	
Sex	9 M/10 F	17 M/11 F	4 M/3 F	ns	
UPDRS-III	12.15 ± 5.1	14.67 ± 6.7	12.04 ± 3.4	ns	
PD symptoms duration, prior diagnosis (mo)	13.0 ± 10.1	14.65 ± 10.9	10.8 ± 1.64	ns	
H&Y stage (n)				ns	
−1	9	11	1		
−1.5	2	5	0		
−2	6	10	5		
−2.5	2	2	1		
Tremoric PD	15	15	3	ns	
Akinetic-rigid PD	4	13	4	ns	
RBD (presence)	0	19	6	< 0.001	A<B; A<C
OH (presence)	0	7	2	0.04	A<B; A<C
MCI (presence)	0	7	7	< 0.001	A<B; A<C; B<C
MMSE	29.47 ± 0.8	28.75 ± 0.9	28.0 ± 1.9	0.008	A>C
GDS	3.11 ± 2.5	4.67 ± 3.4	2.14 ± 2.1	ns	
Constipation (presence)	7	13	4	ns	
^{123}I-FP-CIT-SPECT SBR[b]					
Caudate MAH	2.74 ± 0.9	2.42 ± 0.8	1.95 ± 0.6	ns	
	(−1.69 ± 0.3)	(−1.76 ± 0.3)	(−1.90 ± 0.4)	(ns)	
Caudate LAH	3.09 ± 1.1	2.54 ± 0.8	2.21 ± 0.7	ns	
	(−1.56 ± 0.4)	(−1.71 ± 0.3)	(−1.79 ± 0.4)	(ns)	
Putamen MAH	1.25 ± 0.5	0.95 ± 0.5	0.91 ± 0.3	ns	
	(−2.11 ± 0.2)	(−2.18 ± 0.3)	(−2.12 ± 0.3)	(ns)	
Putamen LAH	1.60 ± 0.6	1.42 ± 0.6	1.25 ± 0.5	ns	
	(−1.97 ± 0.2)	(−1.98 ± 0.3)	(−1.97 ± 0.4)	(ns)	
qEEG					
Posterior MF	8.67 ± 0.9	8.56 ± 0.9	7.70 ± 0.7	0.038	A>C
Anterior MF	7.93 ± 0.8	8.07 ± 0.8	7.48 ± 0.6	ns	
PPF, Hz	9.08 ± 1.2	9.03 ± 1.4	7.5 ± 0.5	0.019	A>C; B>C
Posterior alpha, %	32.35 ± 14.9	41.09 ± 17.8	24.30 ± 12.9	0.033	B>C
Anterior alpha, %	23.49 ± 10.9	31.57 ± 16.3	19.18 ± 11.2	ns	
Posterior beta, %	11.52 ± 7.3	7.23 ± 4.3	7.31 ± 5.2	ns	
Anterior beta, %	11.92 ± 5.5	9.11 ± 5.5	9.35 ± 8.4	ns	
Posterior theta, %	23.74 ± 17.3	25.39 ± 18.1	39.9 ± 18.2	ns	
Anterior theta, %	22.77 ± 12.6	24.65 ± 14.4	35.50 ± 17.7	ns	
Posterior delta, %	6.44 ± 2.4	5.59 ± 1.9	6.47 ± 1.93	ns	
Anterior delta, %	9.65 ± 2.7	7.74 ± 2.5	8.97 ± 2.3	ns	
Posterior sigma, %	8.89 ± 5.0	7.57 ± 5.6	5.62 ± 1.9	ns	
Anterior sigma, %	7.24 ± 2.7	6.38 ± 3.8	5.18 ± 1.5	ns	
Follow-up					
Years	4.65 ± 2.3	5.07 ± 2.3	4.32 ± 1.5	Ns	
MMSE	28.74 ± 1.3	28.28 ± 1.5	24.6 ± 3.7	< 0.001	A>C; B>C
UPDRS-III	14.89 ± 5.5	17.95 ± 6.4	14.75 ± 6.9	Ns	
LED	424.51 ± 216.9	519.0 ± 259.4	549.14 ± 240.7	ns	
Cognitively worsened	6	9	6	0.024	A<C; B<C

Values are shown as mean ± standard deviation.
F, female; GDS, 15-item Geriatric Depression Scale; H&Y, Hoehn and Yahr scale; LAH, less affected hemisphere; LED, levodopa-equivalent dose; M, male; MCI, mild cognitive impairment; MAH, more affected hemisphere; MMSE, Mini-Mental State Examination; OH, orthostatic hypotension; PD, Parkinson's disease; PPF, posterior peak frequency; RBD, REM sleep behavior disorder; SBR, specific binding ratio; UPDRS-III, Unified Parkinson's Disease Rating Scale motor section.
[a]Analysis of variance post hoc comparison (Tukey's method) is shown ($P < 0.05$).
[b]^{123}I-FP-CIT-SPECT SBR reported as computed by BasGan software; *z* scores, adjusted for age and sex, according to the ENC-DAT European normative values,[20] are shown in parentheses.

groups. In addition, the MMSE score was significantly lower in the diffuse/malignant subtype than in the mainly motor subtype. There were no other significant differences among the subgroups, when considering follow-up time, UPDRS-III, and H&Y score, disease duration, and LED.

On DAT-SPECT, especially caudate SBR values were lower in the diffuse/malignant subtype without

reaching statistical significance. qEEG data were significantly different among the groups in the posterior cortical regions: MF, alpha relative band power, and PPF were lower in the diffuse/malignant PD subtype than in the 2 other subtypes.

Prediction of Cognitive Outcome

Table 2 summarizes main baseline clinical, ^{123}I-FP-CIT-SPECT, and qEEG data according to cognitive outcome. PD subtype classification was significantly associated with cognitive outcome ($P = 0.024$). All but one (86%) of the diffuse/malignant patients worsened their baseline cognitive status, whereas only 15 of 47 among the other patients (32%) cognitively worsened at follow-up, with a similar incidence between the mainly motor (6 of 19, 31.5%) and the intermediate (9 of 28, 32.1%) subtypes.

Among neuropsychological tests, CogWorsened patients showed lower baseline phonological verbal fluency, TMT A, and TMT B scores (eTable 1).

Step-wise logistic regression was then applied to a set of independent variables including EEG posterior mean and peak frequency, putamen and caudate SBRs, scores on phonological verbal fluency test and TMT A, age, and disease duration. The selected set of predictors of cognitive outcome consisted of posterior MF and MAH caudate SBRs ($P < 0.0001$). The addition of other potential predictors did not further improve outcome prediction.

Cross-validated (leave-one-out method) ROC analysis results are summarized in Table 3. Posterior qEEG MF achieved 82% accuracy and MAH caudate SBRs achieved 80% accuracy in predicting cognitive outcome. The area under the ROC curve (AUC) did not differ between these 2 metrics. To note, prediction accuracy was lower for age (68%), phonological verbal fluency (65%), TMT A (63%), and TMT B (72%) scores. Figure 1 shows the ROC curves for qEEG posterior MF and MAH caudate SBRs compared with age. Based on these ROC curves, we also computed the cutoff values for both parameters, which were 8.3 Hz for qEEG MF and 2.3 for MAH caudate SBR. The linear model combining these 2 predictors provided a slight increase in accuracy (84%) even if the difference between the AUCs was not significant.

Within cognitively worsened patients, 7 developed dementia. Based on previously selected predictors (ie, qEEG posterior MF and MAH caudate SBRs) these patients could be distinguished from cognitively stable ones with 92.5% accuracy, but they could not be distinguished from the other worsened patients. Patients who developed dementia largely overlapped those with the diffuse/malignant subtype (6 of 7 patients in this group developed dementia).

Survival Analysis

We compared the best predictors of cognitive worsening (posterior qEEG MF and caudate SBR in the MAH) with the clinical classification into 3 PD subtypes toward the timing of worsening.

To this purpose, we divided the patients according to qEEG MF (8.3 Hz) and MAH caudate SBR (2.3) cutoffs. For each predictor, Kaplan-Meier survival curves associated with different groups were compared by the log-rank test. The resulting P values were 0.0024 (Fig. 2A) for the PD subtype, 0.0011 (Fig. 2B) for MAH caudate SBRs, and < 0.0001 for posterior qEEG MF (Fig. 2C). Figure 2D shows the survival curves according to the combination of the 3 predictors. Among the different survival curves, high EEG frequency was particularly associated with long survival time (Fig. 2C), whereas the diffuse/malignant phenotype was associated with early worsening (Fig. 2A). It is worth noting that all but 2 patients in the diffuse/malignant phenotype were also under the threshold for the other 2 predictors.

Discussion

We evaluated a group of de novo drug-naive PD patients and followed them for an average of 5 years. We found that values below the threshold in either baseline mean qEEG frequency in posterior brain regions or nigrocaudate DAT SBR in the more affected hemisphere had good accuracy in predicting patients' cognitive worsening. Baseline PD subtype clinical classification was also moderately related to the cognitive outcome, with patients in the malignant subtype carrying the highest probability to cognitively worsen at follow-up and to develop dementia. Older age, higher H&Y stage, worse TMT and phonological fluency scores, and the presence of RBD at baseline were also significantly correlated with subsequent cognitive decline, but their prediction power was lower, and they did not further improve the accuracy of the model including both the qEEG and the DAT caudate SBR.

Our results are in agreement with previous data showing that increased qEEG low frequencies and decreased high frequencies are correlated with both cognitive dysfunction[33] and PDD.[34] Furthermore, PD patients with decreased qEEG measures of background rhythm were found to have a high risk of cognitive worsening[35] and dementia[6] over time. Moreover, nigrocaudate deafferentation has been related to cognitive impairment in PD,[23,36] and we have already reported that it is a significant predictor of cognitive decline in a smaller sample of de novo PD patients, partially overlapping the present series.[37]

Survival analysis adds some intriguing information that could be informative for prognosis of a given

TABLE 2. Baseline demographic, clinical, ^{123}I-FP-CIT-SPECT, and EEG data in PD patients who were cognitively stable at follow-up (CogStable) and in those who worsened (CogWorsened) their baseline cognitive status

	Follow-up cognitive status		
	CogStable	CogWorsened	*P*
Baseline data			
n	33	21	
Age (y)	66.42 ± 7.7	71.95 ± 5.5	0.003
Education (y)	11.70 ± 4.4	10.71 ± 4.3	ns
Sex	19 M/14 F	11 M/10 F	ns
UPDRS-III	12.51 ± 5.4	14.81 ± 6.3	ns
H&Y stage (n)			0.037
−1	17 (52%)	4 (19%)	
−1.5	5 (15%)	2 (10%)	
−2	8 (24%)	13 (62%)	
−2.5	3 (9%)	2 (1%)	
Tremoric PD	21 (64%)	12 (57%)	ns
Akinetic-rigid PD	12 (36%)	9 (43%)	ns
RBD (presence)	11 (33%)	14 (67%)	0.017
OH (presence)	5 (15%)	4 (19%)	ns
MCI (presence)	8 (24%)	6 (29%)	ns
MMSE	28.98 ± 1.0	28.81 ± 1.4	ns
GDS	3.88 ± 3.0	3.65 ± 3.2	ns
Constipation (presence)	15 (45%)	9 (43%)	ns
PD subtypes			0.024
— Mainly motor	13 (39%)	6 (28.5%)	
— Intermediate	19 (58%)	9 (43%)	
-Diffuse/malignant	1 (3%)	6 (28.5%)	
Follow-up cognition			
— Normal	27 (82%)	0 (0%)	
— MCI	6 (18%)	14 (67%)	
— Dementia	0 (0%)	7 (33%)	
^{123}I-FP-CIT-SPECT SBR[a]			
Caudate MAH	2.84 ± 0.9	1.97 ± 0.4	< 0.001
	(−1.64 ± 0.3)	(−1.92 ± 0.2)	(0.001)
Caudate LAH	3.02 ± 1.0	2.25 ± 0.5	0.002
	(−1.57 ± 0.4)	(−1.81 ± 0.2)	(0.009)
Putamen MAH	1.21 ± 0.5	0.84 ± 0.4	0.004
	(−2.12 ± 0.3)	(−2.18 ± 0.2)	(ns)
Putamen LAH	1.67 ± 0.6	1.17 ± 0.4	0.002
	(−1.93 ± 0.2)	(−2.04 ± 0.3)	(ns)
EEG data			
Posterior MF	8.89 ± 0.8	7.81 ± 0.7	< 0.0001
Anterior MF	8.28 ± 0.7	7.43 ± 0.7	< 0.001
PPF, Hz	9.38 ± 1.3	8.02 ± 1.1	< 0.0001
Posterior alpha, %	41.24 ± 16.2	27.34 ± 15.3	0.001
Anterior alpha, %	32.12 ± 15.3	19.27 ± 9.2	< 0.001
Posterior beta, %	10.62 ± 6.3	5.82 ± 3.9	0.001
Anterior beta, %	11.44 ± 5.6	8.09 ± 6.1	0.02
Posterior theta, %	18.99 ± 13.7	38.82 ± 18.2	< 0.001
Anterior theta, %	19.66 ± 10.8	34.40 ± 15.3	< 0.001
Posterior delta, %	5.48 ± 2.2	6.83 ± 1.9	0.01
Anterior delta, %	8.18 ± 2.9	9.18 ± 2.1	n.s.
Posterior sigma, %	9.29 ± 5.7	5.42 ± 2.7	0.003
Anterior sigma, %	7.41 ± 3.6	5.14 ± 2.2	0.006
Follow-up, y	*4.56 ± 2.3*	*5.24 ± 2.1*	*ns*

Mean ± standard deviation values are shown.
F, female; GDS, 15-item Geriatric Depression Scale; H&Y, Hoehn and Yahr scale; LAH, less affected hemisphere; LED, levodopa-equivalent dose; M, male; MCI, mild cognitive impairment; MAH, more affected hemisphere; MMSE, Mini-Mental State Examination; OH, orthostatic hypotension; PD, Parkinson's disease; PPF, posterior peak frequency; RBD, REM sleep behavior disorder; SBR, specific binding ratio; UPDRS-III, Unified Parkinson's Disease Rating Scale motor section.
[a]^{123}I-FP-CIT-SPECT SBR reported as computed by BasGan software; *z* scores, adjusted for age and sex, according to the ENC-DAT European normative values,[20] are shown in parentheses.

TABLE 3. Cross-validated receiver operating characteristic analysis results

	Posterior qEEG MF			MAH caudate SBRs		
Parameter	Value	Confidence interval		Value	Confidence interval	
ROC AUC	*0.85*	*0.69*	*0.95*	*0.78*	*0.59*	*0.90*
Accuracy, %	82	70	93	80	68	91
Sensitivity, %	84	68	100	84	68	100
Specificity, %	80	64	96	76	59	93
Positive predictive value	0.76	0.58	0.94	0.73	0.54	0.91
Negative predictive value	0.87	0.73	1.00	0.86	0.72	1.00
Positive likelihood ratio	4.21	1.88	9.44	3.51	1.70	7.24
Negative likelihood ratio	0.20	0.07	0.57	0.21	0.07	0.60
Diagnostic odds ratio	21.33	4.42	103.07	16.89	3.63	78.56
Threshold		8.3 Hz			2.3	

The posterior qEEG mean frequency (MF) and the more affected hemisphere (MAH) caudate ^{123}I-FP-CIT-SPECT specific to nondisplaceable binding ratios (SBRs) were used for the prediction of the cognitive outcome (CogStable versus CogWorsened).
AUC, area under curve; ROC, receiver operating characteristic.

patient depending on whether he/she has only the clinical classification or any other biomarkers. For instance, a de novo PD patient with a posterior MF higher than 8.3 Hz is expected to "survive" for a longer time without a significant cognitive worsening, whereas carrying the malignant phenotype (mostly associated with EEG slowing and dopaminergic deficit in this series) predicts earlier deterioration.

If confirmed in larger studies, these findings may be applied in clinical practice. Indeed, EEG is a low-cost and widely available tool, and most equipment automatically provides MF computation. As for ^{123}I-FP-CIT-SPECT, it is increasingly used to confirm a diagnosis[38] in doubtful cases,[39] and nuclear medicine departments largely employ semiquantification tools.[40] Among the latter, we applied one[28] that can be freely downloaded,[41] but others are available. Finally, the

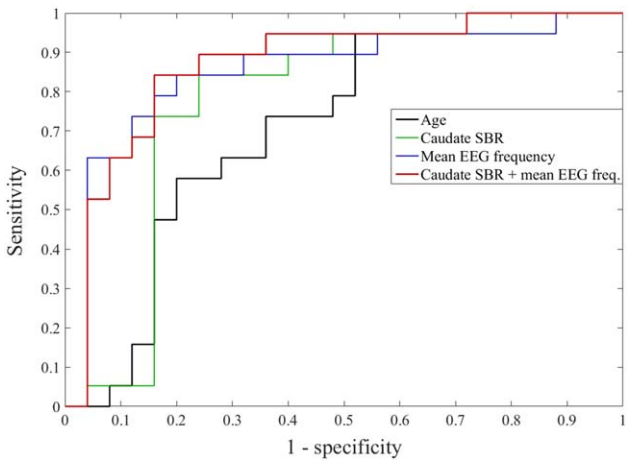

FIG. 1. Cross-validated linear discriminant analysis. Receiver operating characteristic (ROC) curves are shown for qEEG posterior mean frequency (blue line), more affected hemisphere caudate ^{123}I-FP-CIT SBRs (green line), age (black line), and the combination of qEEG posterior mean frequency and more affected hemisphere caudate ^{123}I-FP-CIT SBRs (red line). The *x* axis shows the false-positive rate (1 - specificity), and the *y* axis shows the true-positive rate (sensitivity). [Color figure can be viewed at wileyonlinelibrary.com]

presence/absence of a malignant PD clinical subtype could be easily disclosed based on the presence of MCI, probable RBD, and OH. However, further validation and harmonization of these biomarkers are needed. The reasons for the good accuracy in predicting cognitive outcome that we obtained with both qEEG and DAT-SPECT data could be interpreted in the framework of the "dual hypothesis" of cognitive impairment in PD.[42] This model identified first, mainly dopaminergic-mediated striatofrontal executive dysfunction, characterizing the PD-MCI cognitive profile frequently seen in the early stage of the disease.[42] Paralleling or possibly following the dopaminergic deficit, the model identified cholinergic-based cognitive impairment, especially involved in dementia in later stages.[42] Nigrocaudate dopaminergic dysfunction has been related to executive dysfunction in PD patients,[23,36] thus accounting for the striatofrontal dopaminergic-mediated dysexecutive part of the model. On the other hand, the EEG slowing seems to progressively increase when comparing cognitively intact PD, PD-MCI, and PDD patients.[33,34,43] Normal wake EEG activity, generated by pyramidal neurons under the pacing of intralaminar thalamic neurons,[44] is influenced by cholinergic system integrity, especially in posterior cortical regions.[45] Thus, the progressive EEG slowing found in PD patients with impaired cognitive status has been related to the progressive cholinergic network dysfunction eventually leading to PDD.[46]

According to this hypothesis, the PD cognitive outcome prediction model proposed in the present study may reflect both dopaminergic dysfunction, as shown by nigrocaudate deafferentation (that has been mainly related to dysexecutive MCI), and cholinergic dysfunction, as shown by reduced posterior qEEG mean frequency (that has been mainly related to the risk of dementia).

Latreille and coworkers[7] recently found that EEG slowing ratios during REM sleep and wakefulness

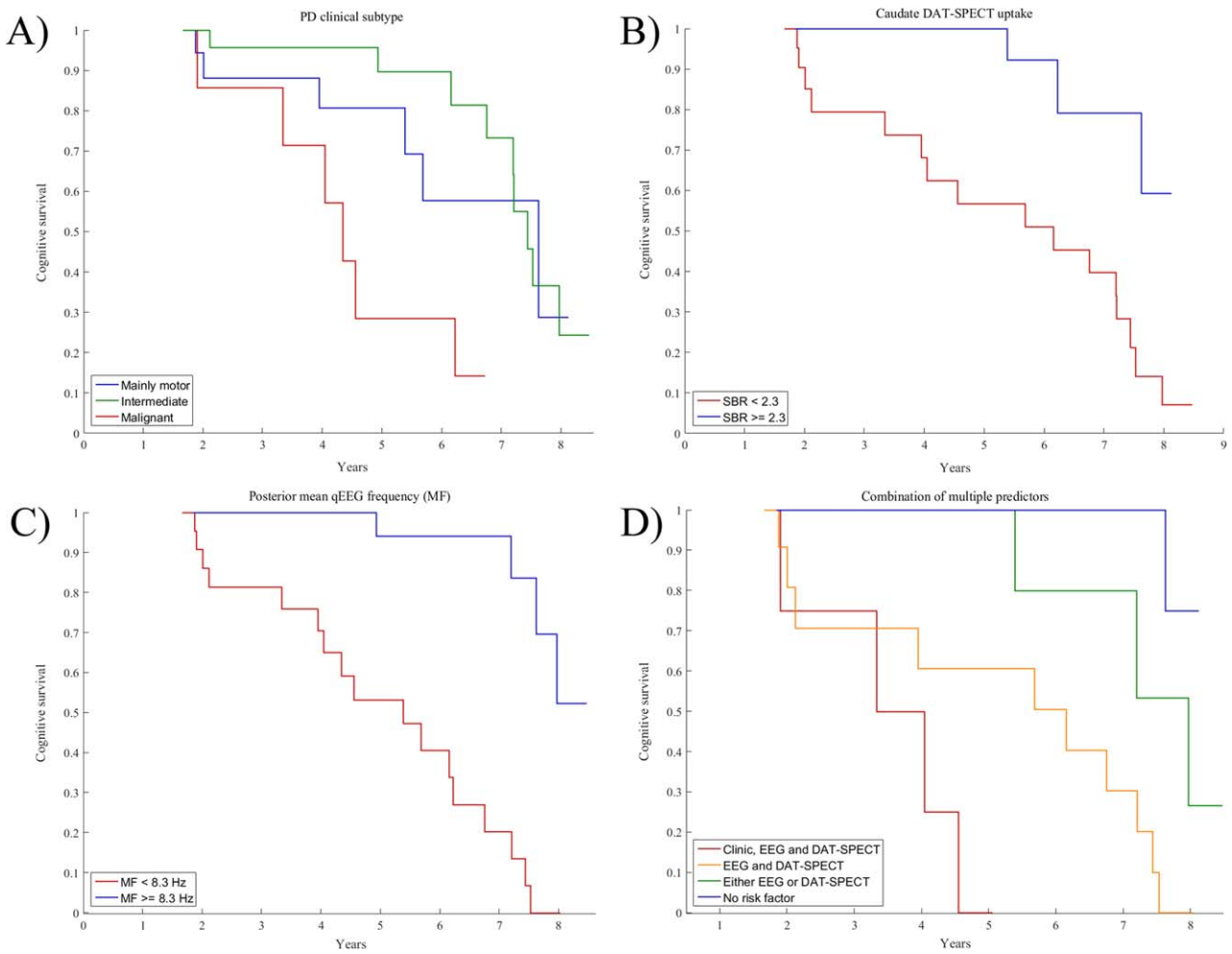

FIG. 2. Kaplan-Meier survival curves for PD clinical subtypes (A), ^{123}I-FP-CIT-SPECT SBR at caudate level (B) with value above or below the threshold in the more affected hemisphere, posterior mean qEEG frequency according to the 8.3-Hz threshold (C). (D) Survival curves are shown according to the combined values over/below threshold of the 2 main predictors along with the presence/absence of the malignant clinical phenotype. Cognitive survival (*y* axis) represents the time elapsed before the shift to a worse cognitive state (MCI or dementia). [Color figure can be viewed at wileyonlinelibrary.com]

could be useful in predicting the development of dementia in PD patients. In keeping with our interpretation, the authors suggested a relationship between EEG findings during both wakefulness and REM sleep and the cholinergic system. Enriching those data,[7] our cross-validated findings exhibited good accuracy in also predicting cognitive worsening other than dementia. Moreover, we provide cutoff values that may be used in clinical practice for both wake EEG and ^{123}I-FP-CIT-SPECT. Reduced background EEG frequencies have been recently found to be related to cortical levels of phosphorylated α-synuclein in posterior cingulate cortex autopsy tissue.[47] The authors suggested that the qEEG measure can be a valuable surrogate biomarker of PD cognitive decline.[47]

Several predictors of dementia in PD, including older age,[48] high UPDRS-III score, low animal fluency test score,[49] the presence of MCI[48] or cognitive deficits,[50] and RBD,[48,51] have been proposed. In the present study, we found several clinical and neuropsychological features that are related to worse cognitive outcome, but all were less accurate compared with both qEEG and ^{123}I-FP-CIT-SPECT.

In the present study, we chose cognitive worsening instead of dementia as the outcome measure, thus preferring a cognitive progression marker rather than a state marker. This approach should account for relevant within-subject modification of the cognitive status over time. In fact, the cognitively worsened group included not only subjects who developed dementia, but also cognitively intact persons who subsequently developed MCI. Although qEEG and DAT-SPECT biomarkers could predict cognitive worsening with good accuracy, they could not distinguish the patients who developed dementia from the other cognitively worsening patients, and only malignant/diffuse phenotype was a strong predictor for dementia. The relatively small sample size, especially of those patients developing dementia (7 subjects), limited the possibility of extendign the analysis by including and

combining more predictors and by deepening subgroup analysis. Indeed, MCI is a heterogeneous entity with several possible outcomes, including remaining stable over time. A dynamic rather than a static outcome that takes into account the baseline cognitive condition seems to be better suited to identify those subjects at high risk of cognitive deterioration compared with those who present a stable cognitive performance over time. Of note, patients with only MCI at baseline tended to remain stable, whereas those with MCI and RBD and/or OH tended to worsen, which highlights the amplification effect of these signs/symptoms within the malignant phenotype.

Moreover, our approach also takes into account those patients who were cognitively normal but who subsequently developed MCI, which has an impact on the ecology of everyday life. However, among the MCI patients, we could not segregate patients with peculiar neuropsychological profiles who might show a different risk of progression to dementia because of the low number of cases in each subclass.

Similar to our approach, a recent work on a large series of PD patients defined a cognitive outcome that included both the emergence of MCI and dementia.[52] In that study, DAT SPECT was one of the most important predictors of cognitive impairment after 2 years of follow-up,[52] in keeping with the present data. The present study adds the notion of the potential of EEG as a predictive factor for cognitive deterioration.

The strength of the present study is that we investigated newly diagnosed PD patients with a comprehensive baseline evaluation, including clinical, brain neurophysiological, and functional neuroimaging assessment, and we followed them for an average follow-up time of 5 years. To the best of our knowledge, this is the first study comparing each clinical risk factor and both neurophysiological and neuroimaging biomarkers to define the best predictors of future cognitive worsening, providing cutoff values to be used in individual subjects.

A significant limitation of the present study is that we had variable instead of fixed follow-up time. However, it was similar both among the 3 PD subtypes and in PD patients with different cognitive outcomes. Another limitation is the previously mentioned limited sample size, in particular concerning the number of patients with the malignant/diffuse phenotype, as evaluated using the classification by Fereshtehnejad et al.[25] The limited sample size drove us to select predictors based on preliminary univariate analysis, which may have influenced results and highlights the need for further studies in larger samples. Finally, whereas qEEG computation is highly reproducible with varied equipment, ^{123}I-FP-CIT-SPECT semiquantification data depend on a reconstruction algorithm and semiquantification tool; thus, the proposed cutoff value may vary using other reconstruction and semiquantification protocols.

In conclusion, we have shown that, in a clinical setting, resting qEEG and ^{123}I-FP-CIT-SPECT in de novo drug-naive PD patients achieve accuracy above 80% in predicting cognitive worsening at an average follow-up time of about 5 years. Moreover, we suggest a PD cognitive outcome prediction model that may be used in individual subjects after validation in larger studies with independent cohorts. The clinical PD subtype classification confirms its importance in predicting cognitive outcome, in particular for the earlier deterioration of patients with the malignant/diffuse phenotype, but for most patients, who were in the mainly motor or intermediate phenotype, our findings highlight the importance of the biomarker approach to PD after baseline evaluation. In particular, this study emphasizes the utility of qEEG, which is a widely available, highly reproducible, and low-cost methodology. ■

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Supporting Data

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