Dementia in Parkinson Disease

A Proton Magnetic Resonance Spectroscopy Study

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Background: Magnetic resonance spectroscopy has been shown to be useful in differentiating idiopathic Parkinson disease (PD) from atypical parkinsonian syndromes such as progressive supranuclear palsy, multiple system atrophy, and corticobasal degeneration.

Objective: To systematically investigate the utility of proton magnetic resonance spectroscopy in distinguishing between idiopathic PD with dementia (PDD) and without dementia.

Design: Group comparisons and correlations of brain metabolites with clinical and neuropsychological variables.

Patients and Methods: Metabolite concentrations were acquired from voxels localized to the basal ganglia and occipital cortex in 14 patients diagnosed as having idiopathic PDD, 12 patients with PD without dementia, and 13 matched control subjects. The 3 groups underwent clinical and neuropsychological assessment.

Results: In the occipital region, N-acetylaspartate levels were significantly reduced in the PDD group relative to the PD and control groups. N-acetylaspartate values correlated with neuropsychological performance but not with severity of motor impairment.

Conclusions: N-acetylaspartate reduction in occipital lobes may be a marker for dementia in PD. The distribution of metabolite reduction differs from that reported in Alzheimer disease. These findings suggest that proton spectroscopy may serve as a metabolic marker of cognitive disturbance in patients with PD.

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Patients with idiopathic Parkinson disease (PD) are 6 times more likely than healthy elderly people to develop dementia.1 Postmortem studies on brains of patients with long-standing PD who later develop dementia (PDD) show both cortical Lewy bodies and Alzheimer-type cortical changes.2 However, Alzheimer-type neuropathological changes do not seem to account for dementia in PD,3 and Lewy body inclusions appear to contribute significantly to cognitive deficits seen in several neuropathological conditions.4

Proton magnetic resonance spectroscopy (1H-MRS) allows the noninvasive, in vivo measurement of brain metabolism. Four major hydrogen-containing metabolites may be identified and measured by means of 1H-MRS. One of these is N-acetylaspartate (NAA),5 which is present in functioning neurons and their processes but absent in mature glial cell cultures,6 and has been taken as a putative neuronal marker. Other metabolites that can be identified are creatine (Cre), related to general metabolism; choline-containing compounds (Cho), which may be altered in processes with increased membrane turnover; and myoinositol (MI), which is mainly contained in glial cells.

Previous studies using MRS in demented patients with Alzheimer disease (AD) showed a consistent pattern of decreased NAA and increased MI values.7-10 In addition, 1H-MRS has been demonstrated to be useful in differentiating multiple-system atrophy from PD11-13 and also PD from progressive supranuclear palsy.13-15 Results from studies comparing patients with PD and normal control subjects are inconclusive, but in general, negative results have been reported for NAA.14,16-18 However, a reduction in the NAA/Cre ratio has been shown in the putamen13 and in the temporoparietal region,19 as have NAA/Cho reductions in the putamen of treated compared with untreated patients with PD, suggesting that Cho levels may be affected by medication.10,20
To our knowledge, only one study has previously examined brain metabolism with the use of $^1$H-MRS, in 4 patients with PDD. These investigators found increased levels of lactate/NAA in the occipital lobe in patients with PDD and PD relative to controls, but no statistically significant differences in NAA/Cr levels among the 3 groups.

The aim of our study was to identify in vivo neurochemical markers associated with dementia in idiopathic PD and their clinical and neuropsychological correlates. We selected 2 brain areas for examination with $^1$H-MRS. The basal ganglia was selected because it is known that striatonigral degeneration is the principal neurochemical correlate of PD. The occipital lobe was selected because altered metabolite concentrations observed with $^1$H-MRS have been reported in the occipital cortex in AD, and also because positron emission tomographic studies have shown metabolic changes in the occipital cortex of patients with dementia with Lewy bodies.

SUBJECTS AND METHODS

SUBJECTS

A total of 42 subjects aged between 54 and 83 years participated in the study. Patients were recruited from an outpatient movement disorders clinic (PD and Movement Disorders Unit, Department of Neurology, Hospital Clinic, Barcelona, Spain) during a 9-month period (November 2000 to July 2001). Subjects were divided into 3 groups. The PDD group consisted of 14 patients with an initial diagnosis of idiopathic PD, who years later developed cognitive decline and fulfilled dementia criteria (see next section, “Diagnostic Criteria and Selection”). The PD group included 14 patients with idiopathic PD who did not meet dementia criteria. The control group consisted of 14 individuals with no history of neurologic disease who were family members or spouses of patients attending the clinic. None of these control subjects met dementia criteria or had parkinsonism. Subjects in all 3 groups were matched for sex and age. The study was approved by the local ethics committee. Written informed consent was obtained from the patients (and, where appropriate, the caregiver) after full explanation of the procedures involved.

DIAGNOSTIC CRITERIA AND SELECTION

Idiopathic PD was diagnosed by means of UK Brain Bank criteria. Care was taken to exclude patients who might have atypical PD syndromes such as progressive supranuclear palsy or multiple-system atrophy, and all patients had a good or excellent initial response to levodopa treatment. To optimize PDD diagnosis, dementia was assessed with 3 standardized instruments: the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, the Clinical Dementia Rating scale, and the Mini-Mental State Examination. Subjects who met dementia criteria exhibited a Clinical Dementia Rating of 1, had a Mini-Mental State Examination score of less than 23, and fulfilled both items specified in the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Subjects who were demented according to some but not all of the rating scales were excluded from the study. No patients who developed dementia before, or within 2 years after, onset of motor symptoms were included in the PDD sample. Additional exclusion criteria for all subjects included the following: history of stroke, cerebral tumor, traumatic brain injury, epilepsy, or psychiatric illness other than depression. Patients with pacemakers or prosthetic implants were excluded, as they could not undergo MRS examination.

Patients were selected according to the following procedure. One investigator reviewed the clinical histories of patients attending the twice-weekly movement disorders clinic. Patients with diagnosed idiopathic PD and suspected or confirmed cognitive decline were interviewed jointly by the investigator and an experienced neurologist. Dementia was assessed with the Mini-Mental State Examination, Clinical Dementia Rating, and Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition. Patients who met criteria for the PDD group were invited to participate in the study. For each patient with PDD recruited, the next patient attending the clinic who fulfilled entry criteria for the PD group, and the next spouse or family member who met criteria for entry into the control group, who were matched for sex and age (±5 years) to the patient with PDD, were interviewed and invited to participate. In this way, 14 triads of PDD-PD-control subjects were obtained. Detailed information from the clinical history was recorded for participating patients, including scores for the Unified Parkinson’s Disease Rating Scale parts I, II, and III; Hoehn and Yahr stage; Schwab and England score; and information about type of parkinsonism (tremor or rigid-akinetic), dyskinesias, motor fluctuations, hallucinations, history of dopaminergic psychosis, details of present medication, and demographics.

NEUROPSYCHOLOGICAL ASSESSMENT

All neuropsychological assessments took place in the morning while subjects in the PD and PDD groups were in a levodopa-induced “off” state. Subjects took the World Health Organization–University of California, Los Angeles, auditory verbal learning test, the forward and backward digit span and block design subtests of the Wechsler Adult Intelligence Scale–Revised, and phonemic, semantic, and action fluency. The Hamilton depression inventory was also administered. Neuropsychological tests were scored in the following way. Two subscores were recorded for the World Health Organization–University of California, Los Angeles, test: (1) difference between the number of words remembered on trial 1 and trial 5 (learning score) and (2) number of words correctly recognized as old at 30 minutes (recognition score). Block design was scored as in Wechsler. Forward and backward digits scores reflected span. Phonemic fluency scores reflected the total words produced beginning with f, a, and s in 1 minute. Semantic fluency was the number of animals named in 1 minute, and action fluency, the number of verbs named in 1 minute. Detailed descriptions of these tests are available in Lezak.

MAGNETIC RESONANCE SPECTROSCOPY

All subjects underwent scanning with a 1.5-T magnetic resonance machine (NV/Cvi 8.4 M4; General Electric Co, Milwaukee, Wis) with a head coil. First, 3-dimensional T1-weighted, inversion recovery spoiled gradient axial images (1.5-mm thickness, 256×256, field of view=24) of the entire brain were obtained for localization purposes. On these, water-suppressed single-voxel spectroscopy (proton brain examination–point resolved spectroscopy [PROBE-PRESS]; repetition time, 1500 milliseconds; echo time, 35 milliseconds; number of excitations, 8; 128 averages) of 2 different brain regions and their corresponding non–water-suppressed signals were obtained. A rectangular voxel (30×20×20 mm) was localized on a T1-weighted axial image, covering as much as possible of the len-
tiform and caudate nuclei (Figure 1A). In patients with PD and
PDD, the voxel was placed contralateral to the most affected side,
and voxel side was alternated for control subjects. Single-voxel
spectroscopy was performed from this location by means of a
semiautomated procedure. Automatic prescan was first ap-
plied, and, if necessary, manual prescanning was also per-
formed. This resulted in all spectra having 6 Hz or less of full
width at half height of the unsuppressed water peak, and per-
centages of water suppression higher than 95%. A second rect-
angular voxel of identical dimensions was then located cover-
ing the occipital cortex of both hemispheres (Figure 1B), and
single-voxel spectroscopy was again performed with the same
settings and procedure. Care was taken to minimize cerebrospi-
nal fluid contamination in both the basal ganglia and occipital
volumes of interest.

All spectra were first visually assessed in a blinded fash-
ion by an experienced investigator. Spectra were evaluated for
general quality depending on the general noise, baseline, wa-
ter suppression, and ability to identify the 4 major metabolic
peaks.

Spectra were postprocessed by means of manufacturer-
provided software (Probe Quantool 2000; General Electric Co).
Curve fitting and line width normalization were performed, and
4 major peaks were identified: NAA, Cre, Cho, and MI. The fit
amplitudes for each peak are reported as “machine numbers,”
these being proportional to metabolite peak areas. Peak ampli-
tudes are referenced to water as an internal standard and are there-
fore proportional to metabolic concentrations (“concentration
equivalents”).

Taking into account the fact that Cre concentrations
may be altered in patients with PD,35 we then adjusted the
concentration equivalents for NAA, Cho, and MI for each
group by means of the β values from the regression of cre-
atine on NAA, and according to the following formula35:
NAA(adjusted) = [NAA(β) – β(β)](observed) – Cre (mean)], where β means each subject.

Statistical analysis was carried out on the concentration-
equivalent NAA values corrected for creatine (“adjusted con-
centration equivalents”). Analyses of variance and regression
analysis were used to determine differences between groups and
the predictive value of neuropsychological and clinical scores.
Scheffe test was used for post hoc comparisons. A P value of
less than .05 was used to test for significance, and all statistical
tests were 2-tailed.

RESULTS

Movement artifact prevented the acquisition of metabo-
lite concentrations from the basal ganglia voxel in 2 pa-
tients with PD, and 1 control subject requested to be with-
drawn from the study midway through the exploration.
Statistical analysis was thus carried out on the remain-
ing 39 subjects (14 with PDD, 12 with PD, and 13 con-
trol subjects). These subjects did not differ in age, years
of education, or Hamilton depression inventory score.
The PD and PDD groups did not differ significantly on
the number of years of evolution of the disease, but they
did differ on mean Hoehn and Yahr stage and on the scores
of the Unified Parkinson Disease Rating Scale scale part
III, with patients with PDD showing more disease sever-
ity on either measure. All patients with PDD either ex-
hibited visual hallucinations at the time of study or were
taking neuroleptic medication to control hallucinatory
symptoms. Mean demographics for all the subjects and
clinical variables for the patient groups are presented in Table 1.

**NEUROPSYCHOLOGICAL PERFORMANCE**

Table 2 shows performance on the neuropsychological tests used. Statistically significant differences among the 3 groups were observed on all tests, and post hoc analysis showed that patients with PDD were impaired relative to both patients with PD and control subjects on all tests. No statistically reliable differences were observed between patients with PD and control subjects on any neuropsychological measures.

**MAGNETIC RESONANCE SPECTROSCOPY**

Table 3 includes the means and SDs for the adjusted values for the different brain metabolites as determined with $^1$H-MRS in the occipital cortex and basal ganglia of the 3 groups.

Adjusted NAA concentration equivalents obtained from the voxel localized to the occipital cortex in the 3 groups studied are plotted in Figure 2. Analysis of variance showed statistically significant differences between the 3 groups ($F_{2,36}=5.00$, $P<.03$), and post hoc tests between the PD and PDD groups achieved statistical significance (Scheffé post hoc = 14.31, $P<.05$). Differences between control subjects and patients with PDD approached significance (Scheffé post hoc = 11.67, $P=.06$).

With only patients with PDD considered, significant Spearman correlations were observed between adjusted occipital NAA and neuropsychological scores on backward digit span and block design tests (Table 4). No correlation was observed with any of the variables reflecting disease severity, either for the PDD group alone or for the PDD and PD groups combined.

No significant differences were found among the 3 groups for the adjusted concentration equivalents for Cho or MI in the occipital cortex, and no significant correlations were observed between these values and any of the clinical or neuropsychological variables in patients with PDD and PD.

In the basal ganglia, analysis of variance showed no significant differences in the adjusted concentration equivalents for the different metabolites among the 3 groups.

**COMMENT**

Metabolite concentrations in the occipital cortex and basal ganglia of patients with PDD were acquired by means of

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**Table 1. Demographics and Clinical Variables**

<table>
<thead>
<tr>
<th>Group</th>
<th>PDD</th>
<th>PD</th>
<th>Control</th>
<th>F/T Statistic</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>70.2 ± 8.44</td>
<td>72.4 ± 6.94</td>
<td>70.0 ± 7.17</td>
<td>0.43</td>
<td>.66</td>
</tr>
<tr>
<td>Years of education</td>
<td>6.62 ± 4.89</td>
<td>7.75 ± 5.29</td>
<td>9.31 ± 4.48</td>
<td>0.99</td>
<td>.38</td>
</tr>
<tr>
<td>Hamilton depression inventory score</td>
<td>3.62 ± 4.61</td>
<td>1.58 ± 2.35</td>
<td>0.62 ± 1.19</td>
<td>2.00</td>
<td>.15</td>
</tr>
<tr>
<td>MMSE score</td>
<td>17.6 ± 5.17</td>
<td>28.5 ± 1.05</td>
<td>29.2 ± 1.17</td>
<td>&lt;.001</td>
<td></td>
</tr>
<tr>
<td>Years of evolution of PD</td>
<td>13.8 ± 5.66</td>
<td>10.83 ± 7.70</td>
<td>NA</td>
<td>0.83</td>
<td>.41</td>
</tr>
<tr>
<td>Hoehn and Yahr stage</td>
<td>3.54 ± 0.95</td>
<td>2.71 ± 0.75</td>
<td>NA</td>
<td>2.46</td>
<td>.02</td>
</tr>
<tr>
<td>UPDRS part I score</td>
<td>5.83 ± 4.61</td>
<td>1.89 ± 1.83</td>
<td>NA</td>
<td>2.42</td>
<td>.03</td>
</tr>
<tr>
<td>UPDRS part II score</td>
<td>22.92 ± 12.69</td>
<td>9.64 ± 5.70</td>
<td>NA</td>
<td>3.18</td>
<td>.004</td>
</tr>
<tr>
<td>UPDRS part III score</td>
<td>36.33 ± 13.81</td>
<td>24.54 ± 12.04</td>
<td>NA</td>
<td>2.24</td>
<td>.04</td>
</tr>
<tr>
<td>Levodopa dose, mg/d</td>
<td>604 ± 216</td>
<td>679 ± 211</td>
<td>NA</td>
<td>1.14</td>
<td>.27</td>
</tr>
</tbody>
</table>

*Data are mean ± SD. PD indicates Parkinson disease; PDD, PD with dementia; MMSE, Mini-Mental State Examination; UPDRS, Unified Parkinson’s Disease Rating Scale; and NA, not applicable.

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**Table 2. Neuropsychological Performance**

<table>
<thead>
<tr>
<th>Neuropsychological Test</th>
<th>PDD</th>
<th>PD</th>
<th>Control</th>
<th>ANOVA $F_{2,36}$</th>
<th>PD vs PDD†</th>
<th>Control vs PDD†</th>
<th>Control vs PD†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Learning</td>
<td>2.87 ± 2.61</td>
<td>4.85 ± 2.26</td>
<td>4.31 ± 1.38</td>
<td>23.01‡</td>
<td>2.83‡</td>
<td>1.97§</td>
<td>0.85</td>
</tr>
<tr>
<td>Recognition</td>
<td>19.82 ± 4.85</td>
<td>25.73 ± 2.57</td>
<td>27.25 ± 2.18</td>
<td>15.22‡</td>
<td>5.91‡</td>
<td>7.43‡</td>
<td>1.52</td>
</tr>
<tr>
<td>Semantic fluency</td>
<td>4.82 ± 4.09</td>
<td>15.00 ± 4.67</td>
<td>17.15 ± 2.97</td>
<td>32.80‡</td>
<td>10.18‡</td>
<td>12.34‡</td>
<td>2.15</td>
</tr>
<tr>
<td>Phonemic fluency</td>
<td>4.36 ± 4.56</td>
<td>8.28 ± 3.76</td>
<td>9.46 ± 3.42</td>
<td>6.15‡</td>
<td>3.92§</td>
<td>5.10‡</td>
<td>1.18</td>
</tr>
<tr>
<td>Action fluency</td>
<td>3.44 ± 4.4</td>
<td>8.31 ± 2.18</td>
<td>10.85 ± 3.29</td>
<td>13.76‡</td>
<td>4.86‡</td>
<td>7.40‡</td>
<td>2.54</td>
</tr>
<tr>
<td>Forward digit span</td>
<td>3.08 ± 1.71</td>
<td>5.25 ± 1.06</td>
<td>5.62 ± 1.12</td>
<td>13.66‡</td>
<td>2.17‡</td>
<td>2.54‡</td>
<td>0.37</td>
</tr>
<tr>
<td>Backward digit span</td>
<td>1.38 ± 1.33</td>
<td>3.17 ± 1.27</td>
<td>3.54 ± 0.78</td>
<td>10.33‡</td>
<td>1.78‡</td>
<td>2.15‡</td>
<td>0.37</td>
</tr>
<tr>
<td>Block design</td>
<td>4.33 ± 5.77</td>
<td>16.00 ± 5.66</td>
<td>20.33 ± 3.17</td>
<td>10.64</td>
<td>2.67‡</td>
<td>3.41‡</td>
<td>0.74</td>
</tr>
</tbody>
</table>

*Unless otherwise indicated, data are mean ± SD. PD indicates Parkinson disease; PDD, PD with dementia; and ANOVA, analysis of variance.
†Post hoc Scheffé test.
‡P<.01.
§P<.05.
1H-MRS and compared with those of patients with PD and control subjects. In the occipital cortex, patients with PDD showed significantly lower NAA values than patients with PD or control subjects. No further significant differences were found in any of the other metabolites in the occipital region or in the basal ganglia among the 3 groups. These results suggest predominantly cortical involvement and are in agreement with positron emission tomography studies demonstrating cerebral hypometabolism in the visual cortices of patients with PDD, in contrast to patients with AD or healthy control subjects.22,23

Our failure to find a difference in metabolite concentrations between patients with PD and control subjects is in agreement with previous studies examining the occipital or basal ganglia regions.14,15,17,21,35 However, Hu et al10 obtained significant NAA/Cre reductions in 17 nondemented patients with PD in a voxel localized to the temporoparietal region. We selected the occipital region because it has been demonstrated to be more sensitive to increases in MI than the parietotemporal region,7 and it has been suggested that, in the pathologic progression of AD, increases in MI precede decreases in NAA.10

Increased MI/Cre and decreased NAA/Cre ratios are a consistent finding in the parietal or occipital cortex of patients with AD.7 We found decreased NAA in the occipital cortex of patients with PDD, suggesting neuronal dysfunction or loss, but no differences in MI values. Shonk et al5 also found that in the occipital cortex of patients with AD, absolute NAA concentrations are reduced and MI levels increased, whereas patients with non-Alzheimer dementia syndromes showed reduced NAA levels but relatively stable concentrations of MI. We propose that MRS may be a useful marker of distinguishing between AD and non-AD dementia. However, further evidence and neuropathological data are needed to confirm this hypothesis.

Increased severity of neurologic symptoms is a risk factor for dementia in PD.37,38 As expected, we found that patients with PDD exhibited greater severity of extrapyramidal symptoms than did patients with PD, reflected by Hoehn and Yahr stage and scores from part III of the Unified Parkinson Disease Rating Scale. However, motor impairment did not correlate with NAA levels in PD or PDD. It is likely that motor impairment in PD is associated with degeneration of the nigrostriatal pathway. However, in the PDD group, we found correlations between NAA values and neuropsychological performance (backward digit span and block design tests). We suggest that the level of NAA in the occipital cortex may serve as a biological marker for the severity of cognitive decline in patients with PDD.

While we observed significantly different occipital NAA values between patients with PD and PDD, post hoc tests showed differences between patients with PDD and control subjects that approached, but did not reach, 2-way statistical significance. Larger studies are needed to confirm this result and to show that patients with PDD can be distinguished from nondemented subjects on the basis of occipital NAA.

In summary, we have shown that patients with PDD have metabolic changes in the occipital cortex indicating predominant neuronal cell dysfunction or death, with little or no glial involvement. These results support the view that PDD is not just the result of AD developing in patients with long-standing PD. In addition, there is a correlation between observed NAA in the occipital cortex and the cognitive status of patients with PDD. Mag-

### Table 3. Adjusted Concentration Equivalents for NAA and MI From the Occipital Cortex and Basal Ganglia*

<table>
<thead>
<tr>
<th>Group</th>
<th>Occipital NAA</th>
<th>Occipital MI</th>
<th>Basal ganglia NAA</th>
</tr>
</thead>
<tbody>
<tr>
<td>PDD</td>
<td>119 ± 12</td>
<td>50 ± 6</td>
<td>99 ± 9</td>
</tr>
<tr>
<td>PD</td>
<td>128 ± 10</td>
<td>53 ± 6</td>
<td>107 ± 16</td>
</tr>
<tr>
<td>Control</td>
<td>126 ± 13</td>
<td>52 ± 7</td>
<td>108 ± 10</td>
</tr>
</tbody>
</table>

*PD indicates Parkinson disease; PDD, PD with dementia; NAA, N-acetylaspartate; and MI, myoinositol.

### Table 4. Correlations Between Adjusted Occipital NAA and Clinical/Neuropsychological Variables in the PDD Sample Alone*

<table>
<thead>
<tr>
<th>Predictor</th>
<th>Spearman Correlation Coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hoehn and Yahr stage</td>
<td>−0.014</td>
</tr>
<tr>
<td>UPDRS part III</td>
<td>−0.373</td>
</tr>
<tr>
<td>Years of evolution</td>
<td>−0.011</td>
</tr>
<tr>
<td>MMSE</td>
<td>0.191</td>
</tr>
<tr>
<td>WHO-UCLA Learning</td>
<td>0.228</td>
</tr>
<tr>
<td>WHO-UCLA Recognition</td>
<td>0.570</td>
</tr>
<tr>
<td>Semantic fluency</td>
<td>−0.116</td>
</tr>
<tr>
<td>Phonemic fluency</td>
<td>0.451</td>
</tr>
<tr>
<td>Action fluency</td>
<td>−0.651†</td>
</tr>
<tr>
<td>Forward digit span</td>
<td>0.297</td>
</tr>
<tr>
<td>Backward digit span</td>
<td>0.576‡</td>
</tr>
<tr>
<td>Block design</td>
<td>0.642‡</td>
</tr>
</tbody>
</table>

*NAA indicates N-acetylaspartate; PDD, Parkinson disease with dementia; UPDRS, Unified Parkinson’s Disease Rating Scale; MMSE, Mini-Mental State Examination; and WHO-UCLA, World Health Organization–University of California, Los Angeles, auditory verbal learning test.
†Significant, 1-tailed P < .05.
‡Significant, 2-tailed P < .05.
netic resonance spectroscopy may be potentially useful in improving the diagnosis of patients with PD who develop dementia.

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Author contributions: Study concept and design (Mr Summerfield and Drs Tolosa, Mercader, Martí, Pastor, and Junqué); acquisition of data (Mr Summerfield and Drs Gómez-Ansón, Tolosa, Mercader, Martí, and Pastor); analysis and interpretation of data (Mr Summerfield and Drs Gómez-Ansón and Junqué); drafting of the manuscript (Mr Summerfield and Drs Gómez-Ansón and Junqué); critical revision of the manuscript for important intellectual content (Mr Summerfield and Drs Gómez-Ansón, Tolosa, Mercader, Martí, Pastor, and Junqué); statistical expertise (Mr Summerfield); obtaining funding (Dr Junqué); administrative, technical, or material support (Drs Gómez-Ansón and Junqué); study supervision (Drs Gómez-Ansón, Tolosa, Mercader, Martí, and Junqué); clinical assessment and acquisition of clinical data (Dr Pastor).

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