(123I) β-CIT and Single-Photon Emission Computed Tomographic Imaging vs Clinical Evaluation in Parkinsonian Syndrome

Unmasking an Early Diagnosis

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Background: The diagnosis of Parkinson disease is currently based on clinical evaluation. Functional neuroimaging using (123I) β-carboxymethoxy-3-β-(4-iodophenyl) tropane (CIT) and single-photon emission computed tomography (SPECT) provides information on the integrity of the dopaminergic system in vivo and is a promising diagnostic tool in early Parkinson disease.

Objective: To evaluate the diagnostic accuracy of dopamine transporter imaging using (123I)β-CIT in patients with suspected parkinsonian syndrome (PS).

Design: Community neurologists referred patients with suspected PS for imaging evaluation. Clinical diagnoses (positive PS or negative PS) were provided by the community neurologists and 2 movement disorder experts. We performed (123I)β-CIT and SPECT imaging, and imaging diagnoses of positive PS or negative PS were assigned. A 6-month follow-up clinical diagnosis was assigned by a movement disorder expert blind to the imaging data, which represented the “gold standard” diagnosis for the study.

Results: Thirty-five patients with suspected PS were referred. Diagnoses in question included essential tremor, psychogenic parkinsonism, drug-induced parkinsonism, primary dystonia, and unspecified gait disorder. Comparing the community neurologist’s diagnoses at referral with the gold standard diagnosis, there was disagreement in 25.7% (sensitivity, 0.92; specificity, 0.30). Comparing the quantitative imaging diagnoses with the gold standard, there was disagreement in 8.6% (sensitivity, 0.92; specificity, 1.00).

Conclusion: Performing (123I)β-CIT and SPECT imaging at baseline appears to be a useful diagnostic tool to detect patients thought to have PS at baseline but who, after follow-up, do not have PS.

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The diagnoses of Parkinsonian syndrome (PS) and Parkinson disease (PD) are currently based on clinical evaluation. The most widely accepted clinical definition of PD requires the presence of 2 of 3 cardinal motor signs (tremor, rigidity, and bradykinesia) and a response to levodopa. Long-term clinicopathologic studies evaluating the diagnostic accuracy of PD demonstrate that the diagnoses most commonly mistaken for PD are progressive supranuclear palsy and multiple system atrophy. However, early in its course, the diagnoses most commonly mistaken for PD include essential tremor, vascular parkinsonism, drug-induced parkinsonism, and Alzheimer disease. In addition, subtle parkinsonian symptoms are relatively common in elderly subjects making the diagnosis especially challenging. Retrospective studies have shown that up to 29% of patients initially diagnosed with PS by primary physicians are misdiagnosed.

Misdiagnosing other conditions as PS may lead to futile therapy with dopamine-replacing agents, often resulting in unnecessary adverse effects. In addition, significant resources are spent on computed tomography or magnetic resonance imaging of the brain, which are obtained to rule out other less likely etiologies of the parkinsonian symptoms. There is a clear need for a more definitive diagnostic test to “rule in” a diagnosis of PS that is more accurate than the initial clinical examination early in the course of the disease.

Recent studies demonstrate that movement disorder experts (MDEs) may also misdiagnose PD early in its course when recruiting subjects for early PD clinical trials. In the REAL-PET study, comparing ropinirole hydrochloride and levodopa as initial treatments in untreated patients, 21 (11%) of 193 enrolled subjects had positron emission tomographic scans without evidence of reduction in fluorodopa F 18 uptake at baseline and after 2 years. In the ELLDOPA study,
paring initial levodopa therapy with a placebo in recently diagnosed patients, 21 (14%) of 142 enrolled subjects had scans without evidence of reduction in \( {^{123}}\text{I})\text{-carboxymethoxy-3-}\beta\text{-}(4\text{-iodophenyl})\text{ trope (CIT) uptake at baseline and again at 9 months (19/19; 2 terminated).}

Neuroimaging studies have demonstrated that dopamine transporter (DAT) ligands in association with single-photon emission computed tomographic (SPECT) or positron emission tomographic imaging identify individuals with PD and PS and distinguish them from healthy subjects or individuals with movement disorders not associated with dopamine depletion.\(^{11-15}\) The overall goal of this study was to evaluate DAT imaging using \(^{123}\text{I})\text{-CIT and SPECT as a diagnostic tool in patients with early parkinsonian symptoms suspected to have PS but in whom there was diagnostic uncertainty.}

**METHODS**

**SUBJECTS**

Community neurologists identified patients with suspected PS but in whom they had diagnostic uncertainty. Parkinsonian syndrome was defined as PD and related striatal dopamine-deficient syndromes including progressive supranuclear palsy, multiple system atrophy, striatal nigral degeneration, and corticobasal ganglionic degeneration. All subjects gave written informed consent after it was clear that the nature and consequences of the study were understood.

**CLINICAL DIAGNOSES**

The community neurologists completed a clinical diagnostic form documenting a working diagnosis (positive PS or negative PS) and diagnostic certainty at the time of referral. Subjects were evaluated clinically by 2 MDEs prior to imaging, and each provided a working diagnosis. One MDE (MDE 1) had access to the imaging data and provided information regarding the imaging to the subject and community neurologist, while the second MDE (MDE 2) remained blind to the imaging data. The second MDE reevaluated the subject after 6 months and assigned a final clinical diagnosis, which was the “gold standard” diagnosis for this study. A schematic outlining the study visits is provided in **Figure 1**.

**IMAGING DIAGNOSES**

Subjects underwent \(^{123}\text{I})\text{-CIT and SPECT imaging within 1 month of their initial clinical evaluation. The radiopharmaceutical \(^{123}\text{I})\text{-CIT was produced and SPECT imaging studies were obtained as previously described.}\(^{16,17}\)**

**IMAGING ANALYSIS**

A nuclear medicine expert and technician who were blind to the clinical data analyzed the imaging data. A visual imaging diagnosis of “positive for PS” or “negative for PS” was assigned to each image based on review of the pattern of striatal uptake of \(^{123}\text{I})\text{-CIT (Figure 2). The primary quantitative imaging outcome measure, the specific nondisplaceable striatal uptake

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**Figure 1.** Schematic of study design and visit schedule. MDE indicates movement disorder expert.

**Figure 2.** \(^{123}\text{I})\text{-Carboxymethoxy-3-}\beta\text{-}(4\text{-iodophenyl})\text{ trope and single-photon emission computed tomographic scans from a healthy control and a subject with Parkinson disease.}
(V3′), was determined through a standardized analysis method previously described. Studies have demonstrated an age-related decline in V3′. To adjust for age, V3′ for each subject was compared with an existing database of 73 healthy controls (aged 24 to 88 years). Healthy controls underwent a neurological examination and a review of family history to ensure that there were no signs or risk factors of PD. Data were age-corrected by fitting a regression line to the lowest putamen data of the healthy controls and correcting V3′ data from the study subjects with a regression function. Age-corrected data were expressed as a percentage of age-expected V3′ value. Those with a decrease in DAT density of greater than 30% were considered to have dopaminergic neuronal degeneration and given the diagnosis of positive PS based on quantitative imaging. A loss of greater than 30% from the healthy controls appears to be a reasonable definition for positive PS based on our experience with other studies involving early subjects with PD.

STATISTICAL ANALYSIS

The sensitivity, specificity, and area under the curve for the clinical diagnoses assigned by the community neurologists, MDEs, and imaging diagnoses were calculated against the gold standard diagnosis (area under the curve, 0.5 [sensitivity + specificity]). Interrater reliability using the κ coefficient was calculated.

RESULTS

DEMOGRAPHICS

Fourteen community neurologists referred 37 patients with a diagnosis of suspected PS during a 12-month period. Two subjects were eliminated from the analysis; the first had an uninterruptible scan with motion artifact, and the second was lost to follow-up. The mean diagnostic certainty at baseline for the community neurologists was 71.7% and for the MDEs, 82.7%. The demographic characteristics for the 35 subjects, based on the MDEs’ evaluation at the baseline visit, are listed in Table 1.

INITIAL DIAGNOSES

Community neurologists and MDEs assigned a diagnosis of positive PS or negative PS at baseline, prior to the imaging study (Figure 3). The diagnosis of the community neurologists at the time of referral was positive PS in 30 of 35 patients. The initial diagnosis of positive PS was assigned by MDE 1 in 31 of 35 cases and by MDE 2 in 25 of 35 cases. There was disagreement among the community neurologists and the initial clinical diagnosis of MDE 1 in 7 of 35 cases, the diagnosis of MDE 2 in 9 of 35, the visual imaging diagnosis in 12 of 35, and the quantitative imaging in 12 of 35. The visual and quantitative imaging diagnoses disagreed in 3 of 35 cases.

COMPARISON WITH THE GOLD STANDARD DIAGNOSIS

One outcome of this study was to compare the clinical diagnoses and the imaging diagnoses with the gold standard clinical diagnosis at the 6-month follow-up visit. Of the 35 subjects who completed the study, the gold standard diagnosis was positive PS in 25 cases and negative PS in 10 cases.

Comparing the diagnosis of the community neurologist at referral with the gold standard diagnosis, there was disagreement in 9 (25.7%) of 35 cases. The baseline diagnoses of MDE 1 and MDE 2 disagreed with the gold standard in 7 (20.0%) of 35, on average.
Imaging diagnoses with the gold standard diagnosis, there was disagreement in 3 (8.6%) of 35 cases for the visual imaging diagnosis and 2 (5.7%) of 35 for the quantitative imaging diagnosis (Figure 4). Other diagnoses assigned by the gold standard included: essential tremor (5), psychogenic parkinsonism (2), primary dystonia (2), and drug-induced parkinsonism (1).

The interrater reliability for the clinical evaluators and the imaging are shown in Table 2. The sensitivity, specificity, and area under the curve for the clinical and imaging diagnoses using the gold standard diagnosis as the reference are shown in Table 3.

**COMMENT**

Performing (123)I-B-CIT and SPECT imaging is a useful tool to distinguish between individuals with PS, including PD and other atypical forms of parkinsonism, from those without PS.13,14,21 The goal of this study was to test the diagnostic accuracy of DAT imaging in patients with an uncertain diagnosis, the population in which a diagnostic test for PS would be most useful.

In this study, there was substantial disagreement between the DAT imaging diagnosis and clinical diagnosis for both the primary neurologists and the MDEs. It should be emphasized that the population studied represents difficult-to-diagnose cases and does not represent all patients diagnosed with PS. There appears to be increased congruency between the clinical and imaging diagnoses at the 6-month follow-up evaluation (gold standard diagnosis in this study) suggesting that (123)I-B-CIT and SPECT imaging at baseline can detect those subjects who were thought to have PS at baseline but who, after follow-up, do not have PS.

Table 2. Interrater Reliability for the Clinical Evaluators and Imaging*

<table>
<thead>
<tr>
<th>Referring Neurologist</th>
<th>MDE 1 (Unblinded)</th>
<th>MDE 2 (Blinded)</th>
<th>Visual Analysis</th>
<th>Quantitative Analysis</th>
<th>Gold Standard (MDE 2)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MDE 1 (unblinded)</td>
<td>0.11 (−0.29 to 0.50)</td>
<td>0.26 (−0.34 to 0.26)</td>
<td>0.15 (−0.18 to 0.47)</td>
<td>0.54 (0.21 to 0.87)</td>
<td>0.49 (0.17 to 0.82)</td>
</tr>
<tr>
<td>MDE 2 (blinded)</td>
<td>0.26 (−0.34 to 0.26)</td>
<td>0.26 (−0.08 to 0.80)</td>
<td>0.15 (−0.18 to 0.47)</td>
<td>0.54 (0.21 to 0.87)</td>
<td>0.49 (0.17 to 0.82)</td>
</tr>
</tbody>
</table>

Table 3. Sensitivity, Specificity, and Area Under the Curve for the Clinical and Imaging Diagnoses Using the “Gold Standard” Diagnosis as the Reference*

<table>
<thead>
<tr>
<th>Diagnosis</th>
<th>No. of Patients With PS</th>
<th>No. of Patients Without PS</th>
<th>Sensitivity</th>
<th>Specificity</th>
<th>Area Under the Curve</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary neurologist baseline</td>
<td>23</td>
<td>7</td>
<td>0.92</td>
<td>0.3</td>
<td>0.61</td>
</tr>
<tr>
<td>No PS</td>
<td>2</td>
<td>3</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unblinded MDE 1 baseline</td>
<td>24</td>
<td>7</td>
<td>0.96</td>
<td>0.3</td>
<td>0.63</td>
</tr>
<tr>
<td>PS</td>
<td>24</td>
<td>7</td>
<td>0.96</td>
<td>0.3</td>
<td>0.63</td>
</tr>
<tr>
<td>No PS</td>
<td>3</td>
<td>7</td>
<td>0.88</td>
<td>0.7</td>
<td>0.79</td>
</tr>
<tr>
<td>Blinded MDE 2 baseline</td>
<td>22</td>
<td>3</td>
<td>0.88</td>
<td>0.7</td>
<td>0.79</td>
</tr>
<tr>
<td>PS</td>
<td>22</td>
<td>3</td>
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<td>0.7</td>
<td>0.79</td>
</tr>
<tr>
<td>No PS</td>
<td>3</td>
<td>7</td>
<td>0.88</td>
<td>0.7</td>
<td>0.79</td>
</tr>
<tr>
<td>Visual imaging analysis</td>
<td>24</td>
<td>2</td>
<td>0.96</td>
<td>0.8</td>
<td>0.88</td>
</tr>
<tr>
<td>PS</td>
<td>24</td>
<td>2</td>
<td>0.96</td>
<td>0.8</td>
<td>0.88</td>
</tr>
<tr>
<td>No PS</td>
<td>1</td>
<td>8</td>
<td>0.96</td>
<td>0.8</td>
<td>0.88</td>
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<tr>
<td>Quantitative imaging analysis</td>
<td>23</td>
<td>0</td>
<td>0.92</td>
<td>1.0</td>
<td>0.96</td>
</tr>
<tr>
<td>PS</td>
<td>23</td>
<td>0</td>
<td>0.92</td>
<td>1.0</td>
<td>0.96</td>
</tr>
<tr>
<td>No PS</td>
<td>2</td>
<td>10</td>
<td>0.92</td>
<td>1.0</td>
<td>0.96</td>
</tr>
</tbody>
</table>

Abbreviations: MDE, movement disorder expert; PS, parkinsonian syndrome.
* Values are expressed as probabilities.
The sensitivity and specificity data in Table 3 demonstrate the following: (1) The community neurologist’s initial diagnosis is highly sensitive. There was only 1 false-negative case in which the community neurologist diagnosed negative PS and the gold standard diagnosis was positive PS. (2) Seven patients diagnosed with positive PS by the community neurologists had negative PS based on the 6-month gold standard diagnosis, and thus, there were several false-positive diagnoses by community neurologists. (3) In those cases diagnosed with positive PS by the community neurologist and negative PS by the gold standard, the quantitative imaging diagnosis agrees with the gold standard in all cases (7/7). (4) The quantitative imaging diagnosis offers more specificity (fewer false-positive cases) compared with the visual imaging analysis. (5) There were no subjects with a false-negative imaging diagnosis (positive PS by quantitative imaging and negative PS by the gold standard). Two subjects had a false-negative quantitative imaging diagnosis at the 6-month follow-up visit (negative quantitative imaging diagnosis with a positive clinical diagnosis). (6) The quantitative imaging diagnosis appears to have a similar sensitivity to the clinical examination, though with more acceptable specificity. Dopamine-transporter imaging appears to improve diagnostic accuracy in early PS.

This study demonstrates that (123I)β-CIT and SPECT imaging at baseline can detect those subjects who were thought to have PS but who, after follow-up, do not have PS. This population represents patients who may be inappropriately treated or inadvertently selected for PD-related trials. Diagnostic uncertainty remains for those 2 individuals who were diagnosed with negative PS by imaging but positive PS at the 6-month follow-up examination. The diagnoses of these individuals will be better understood with longer-duration follow-up.

We recognize that there are several limitations to this preliminary study. Longer follow-up is necessary to determine a more definitive final clinical diagnosis. However, even at the 6-month follow-up visit, there was increased congruency between the quantitative imaging diagnosis and the clinical gold standard diagnosis. In this study, the subjects were not blinded, and it is possible that this compromised the blind of the MDE at the 6-month follow-up visit. The sample size of the study was modest, and more subjects need to be studied to accurately determine the percentage loss in (123I)β-CIT uptake that is necessary to confirm a diagnosis of PS. We have modified the study protocol to extend the duration of follow-up, ensure the blind is maintained, and expand the sample size in an ongoing follow-up study.

A diagnostic test for PD may have different requirements depending on the setting in which it is intended for use. In this study, we have chosen to use (123I)β-CIT and SPECT imaging as a “rule in” test confirming the presence of PS with a low false-negative rate, as it is important not to overlook any case with PS and to define clearly the range of (123I)β-CIT uptake in those with PS. However, in a medication trial in which the study medication may have significant adverse effects, it would be important to use this diagnostic tool as a “rule out” test with high sensitivity to exclude any subjects without PS and therefore would require a low false-positive rate.

As clinical therapeutics in Parkinson disease have developed, the need for in vivo markers of degeneration has rapidly expanded. Despite significant advancements in our understanding of the pathophysiology of PD, there is no widely accepted diagnostic test for PD. Practicing neurologists and research investigators continue to rely on a diagnosis based on clinical examination, which lacks specificity. The data from this study suggest that DAT imaging using the radioligand (123I)β-CIT and SPECT is a useful diagnostic tool at the time that parkinsonian symptoms occur. In this small cohort, the use of (123I)β-CIT and SPECT as a diagnostic test appears to address the current clinical need to provide patients and physicians with a more accurate diagnosis.

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**Correction**

Incomplete Closing Paragraph. In the Editorial titled “Genes for Movement” by Roger N. Rosenberg, MD, published in the July issue of the ARCHIVES (2004;61:1006), a technical error occurred during file conversion and final sentences were omitted. The editorial is reprinted in the August issue and is available free at the ARCHIVES’ Web site: http://ama-assn.org/cgi/content/full/61/7/1006. The ARCHIVES regrets the error.