The Coalition Against Major Diseases: Dopamine Transporter Neuroimaging as an Enrichment Biomarker To Enable Parkinson’s Disease Clinical Trials

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Introduction

• Critical Path Institute’s Coalition Against Major Diseases is supported by grant No. U01FD003865.

• Reduced levels of dopamine transporter (DAT) assessed by SPECT are thought to be an early marker of Parkinson's disease (PD) and are often used to support drug development in PD.

• Patients identified as SWEDDs (Suspected Without Evidence of Dopaminergic Deficit) have clinical signs and symptoms of PD, but their DAT scans on SPECT imaging are indistinguishable from those of age-matched controls and represent a reliable indicator that presynaptic dopaminergic deficits are absent.

• These analyses suggest that in suspected PD patients, reduced levels of DAT assessed by SPECT imaging correlate with known Parkinson’s disease (PD) pathology and functional impairment.

• The authors gratefully acknowledge the project support of Steve Angersbach, Robin Shane, and Marshall, VL, et al. (2009). Parkinson’s disease is

Background

- The Coalition Against Major Diseases (CAMD) was formed by the Critical Path Institute in response to FDA’s Critical Path Initiative (Romero et al., 2010, 2011). The CAMD PD Biomarkers Team plans to seek regulatory qualification of biomarkers to support effective, drug development in PD.

- Limitations: D

Objective

- To qualitatively reduce in DAT levels assessed by SPECT as an enrichment biomarker for clinical trials in early onset PD.

Methods

- We assessed the % of SWEDDs in patients in PD trials, including ELDDOA, PRECEPT, and REAL-PEL (all de novo), CALMPOD (start of dopaminergic therapy) and GP14145 (treated with stable response).

- A literature review was conducted to identify observational and clinical studies of first diagnosis patients that utilized DAT imaging with longitudinal follow up, blinded imaging analyses, relevant statistics, and defined ligands (Duusan’sn 18F) or FP-CIT or B-CIT.

- Four studies were identified that fulfilled the criteria and each study was further analyzed to define DAT imaging’s specificity, positive predictive value (PPV), and negative predictive value (NPV), calculated with 95% confidence intervals (Clapper and Pearson method, Clapper and Pearson, 1994).

- Nine separate comparisons of DAT imaging in patients with PD vs. essential tremor, or vascular, drug-induced, or other secondary Parkinsonisms, were evaluated with visual or quantitative interpretation of DAT images vs. the “gold standard” clinical diagnosis by movement disorder experts.

- To understand the relationship between the results from the different studies and to give an estimate of an overall level of sensitivity and specificity, a meta-analysis was performed taking a single comparison from each study (it would not be possible to use multiple comparisons from the same study).

Results

- The overall estimate of sensitivity and specificity is shown as the large point and the shape is a 95% confidence interval for the combined sensitivity-specificity. Note that in Fig. 5, the 95% confidence interval for the combined sensitivity-specificity is an ellipse, with the different selection of combinations in Figs. 6 it has collapsed to a line. This is underestimating the true uncertainty and is an artifact due to performing the analysis on a limited number of comparisons.

- These examples showed a significant level of heterogeneity between the studies; i.e., the differences between the studies were greater than possible by chance alone. However given the differences in study design such as the length of follow up time, this may not be surprising.

- Statistical parameters of DAT neuroimaging identified patients with PD and other primary parkinsonian syndromes and supported a robust and reliable method for discriminating PD from essential tremor and drug-induced, or other secondary parkinsonisms, that may have scans without evidence of dopamine deficiency (SWEDDS).

- Sensitivity ranged from 68-96% and specificity from 74-100% (with one outlier).

- Limitations: Differences in the study design (e.g. length of follow-up) and neurobiology likely contributed to this heterogeneity.

Conclusions

- These analyses suggest that in suspected PD patients, reduced levels of DAT assessed by SPECT can discriminate PD from essential tremor and certain secondary parkinsonisms without rigorous investigation.

- Such data support the use of DAT imaging to enable identification of a target patient population for enrollment of clinical trials with idiopathic PD patients.

References


- Marshall, VS; et al. (2009). Parkinson's disease is overdiagnosed clinically at baseline in diagnostically uncertain cases: a 3-year European multicenter study with repeat [123I]-FP-CIT/PET. Mov Disord., 24, S80-S88.


Disclosures

- The authors gratefully acknowledge the project support of Steve Angersbach, Robin Shane, and Deanna Sanchez of Critical Path Institute, and Dr. Louis Kirby for contributions to this work. We also acknowledge the advice and collaboration from Dr. Marc Walton of FDA, Office of Translational Sciences.

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Key to Abbreviations

- AP5-Atypical Parkinson Syndrome
- NC—Normal Control
- PD—Parkinson’s Disease
- ET—Essential Tremor
- PS—Parkinson Syndrome
- MSA—Multiple System Atrophy
- PSP—Progressive Supranuclear Palsy
- DBL—Dystonia Body Disease
- DP—Drug Induced Parkinsonism
- G5—Gold standard (clinical diagnosis)