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13. ABSTRACT ***(Maximum 200 Words)***

The primary goal of this study is to investigate whether sequential dopamine transporter imaging using [^{123}I]β-CIT and SPECT, a marker of dopamine terminal integrity, will provide a quantitative biomarker of Parkinson's disease progression in subjects with early Parkinson's disease during a nine month imaging interval. The subjects in this study are a subset of an NIH funded clinical trial called ELLDOPA, designed to examine the effect of L-dopa on the rate of progression of Parkinson's disease. All subjects have been and will be recruited and clinically evaluated through their participation in that study. During the first and second grant year, 127 subjects recruited from 31 ELLDOPA study sites have undergone their baseline [^{123}I]β-CIT/SPECT scan and 94 have undergone their nine month scan. This study will directly evaluate in vivo the rate of ongoing dopaminergic neuronal degeneration in early Parkinson's disease, whether the rate of neuronal degeneration is affected by L-dopa, a potential neurotoxin, and whether the changes in imaging uptake correlate with clinical measures of disease progression? Finally we will use [^{123}I]β-CIT and SPECT imaging to investigate the role of the dopamine transporter in the development of neurotoxicity from L-dopa and related compounds.

14. SUBJECT TERMS
Parkinson's, SPECT, Beta-CIT, Dopamine, neurotoxin, ELLDOPA

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INTRODUCTION

In this project we propose to use in vivo imaging of the dopamine transporter as a quantitative biomarker of dopamine neuronal loss to measure the rate of progressive neuronal degeneration in subjects with early Parkinson's. In previous studies we have demonstrated that ß-CIT/SPECT imaging of the dopamine transporter is a quantitative biomarker for Parkinson's disease onset and disease severity disease [1-3]. The subjects in this study will be a subset of an NIH funded clinical trial called ELLDOPA, designed to examine the effect of L-dopa on the rate of progression of Parkinson's disease. All subjects have been and will be recruited and clinically evaluated through their participation in that study. The imaging study proposed in this grant will enhance that clinical study by providing a secondary outcome measure in addition to clinical evaluation to assess disease progression. Moreover, these imaging studies will directly evaluate in vivo the rate of ongoing dopaminergic neuronal degeneration in early Parkinson's disease, whether the rate of neuronal degeneration is affected by L-dopa, and whether this correlates with clinical measures of disease progression?

BODY

During the past two years we have made substantial progress on this project. The primary goal of this study is to investigate whether sequential dopamine transporter imaging using [123I]ß-CIT and SPECT, a marker of dopamine terminal integrity, will provide a quantitative biomarker of Parkinson's disease progression in subjects with early Parkinson's disease. The subjects in this study will be a subset of an NIH funded clinical trial called ELLDOPA, designed to examine the effect of L-dopa on the rate of progression of Parkinson's disease. All subjects have been and will be recruited and clinically evaluated through their participation in that study.

The proposed hypotheses in the study are:

1: Striatal [123I]ß-CIT uptake will be significantly reduced in sequential SPECT imaging during a nine month interval in early Parkinson's disease.

Subjects will be recruited from in the ELLDOPA study within two years of diagnosis. The relative reduction in [123I]ß-CIT uptake in the caudate and putamen and in the side ipsilateral and contralateral to initial symptoms will be compared. The progressive loss of [123I]ß-CIT uptake, a measure of transporter integrity, will demonstrate the progression of dopaminergic terminal loss in Parkinson's disease showing that neurodegeneration is an ongoing process in this disorder [4-6]. The alternative hypothesis would be that dopaminergic terminal loss in Parkinson's disease is the result of transient insult coupled with age related loss of dopaminergic neurons [7, 8].

2: The rate of reduction in [123I]ß-CIT uptake in sequential SPECT imaging during a nine month interval will be increased in those patients on L-dopa compared to a group of patients on placebo.

While L-dopa remains the most widely used and generally most effective treatment for Parkinson's disease, recent evidence has raised the concern that L-dopa may be toxic to catecholaminergic nerve cells and may therefore contribute to progression of Parkinson's disease [9]. [123I]ß-CIT SPECT imaging will provide a direct measure of dopaminergic degeneration in subjects on L-dopa or placebo. Changes in clinical rating scales will be compared to changes in [123I]ß-CIT uptake in sequential scans. Prior imaging studies have demonstrated that L-dopa does not significantly regulate the imaging outcome measure [10].

3: The rate of reduction in [123I]ß-CIT uptake in sequential SPECT imaging during a nine month interval will correlate with the dopamine transporter density measured in the first scan.

Preliminary data indicates that loss of [123I]ß-CIT uptake in sequential SPECT imaging during the first two years following diagnosis is greater in subjects with relatively high levels of dopamine transporters at or near the time of diagnosis. This suggests that the dopamine transporter may be important in the etiology and progression of Parkinson's disease possibly as a gate for neurotoxins [11].

During Year 1 and 2 of this grant our primary goal has been to recruit subjects and complete their baseline [123I]ß-CIT /SPECT scan and to complete the nine month follow-up scan. In March, 2001 the principal investigator and all study personnel moved from Yale University to the Institute for Neurodegenerative Disorders. The Institute for Neurodegenerative Disorders has all resources and facilities necessary to complete all aspects of the study. The current study has been relinquished by Yale University and the Institute for Neurodegenerative Disorders is in the process of appropriate submission to obtain the funding to complete the study. The Institute for Neurodegenerative Disorders has established a comprehensive clinical neuroimaging center for Parkinson's disease patients and has developed the practical methods to ensure that patients are imaged effectively and treated appropriately during their participation at our center. We have worked closely with the 36 participating sites in the ELLDOPA study and with the coordinating center of the clinical study at the Parkinson Study Group. Drs. Marek and Seibyl have met with the ELLDOPA steering committee and with the study biostatistician (Dr. Oakes) every 3 months. At the study initiation we held a meeting in New Haven for the study coordinators from all sites participating in the ELLDOPA study to review the imaging study and all study procedures including recruitment. Our imaging study project coordinator is in frequent contact with the ELLDOPA chief coordinator for the Parkinson Study Group and with the site coordinators.

During the past two years, 127 subjects have undergone their baseline and 94 subjects have undergone their nine month [123I]ß-CIT /SPECT scan. These individuals have been recruited from 31 sites throughout the US and Canada. The total number of subjects who will be enrolled in the ELLDOPA study is 360. We have recruited approximately 60% of the possible subjects. Therefore, we anticipate that we will recruit a total of approximately 145-155 subjects. In addition data from this study has shown that our retention rate of subjects for the repeat scan is about 95%. Therefore, we anticipate that we will meet our goals for 140 -150 subjects for scan 2 during the third year of the grant.

During years 1 and 2 there have been no severe or serious adverse events due to subject participation in the imaging study. The ELLDOPA treatment assignment of all subjects in the imaging study has remained masked. The imaging data will be analyzed and the imaging database and clinical ELLDOPA database merged (as detailed in the study plan) after all subjects have undergone their second [123I]ß-CIT /SPECT scan.

KEY RESEARCH ACCOMPLISHMENTS

YEAR 1 AND 2

- 127 Subjects recruited from 31 sites for their baseline [123I]ß-CIT /SPECT scan.
- 94 Subjects undergone nine month [123I]ß-CIT /SPECT scan

REPORTABLE OUTCOMES

None – Study is in the recruitment phase and data acquisition phase.

CONCLUSIONS

None – Study is in the recruitment phase and data acquisition phase.

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