Parkinson’s Disease in the Elderly and in Aging: Clinical, Genetic, and Neurobiological Substrates

Background and Significance

Aging is the unexplored catalyst for Parkinson’s Disease and for Alzheimer’s Disease

While the prevalence of Parkinson’s disease (PD) in the community residing elderly is impressive (~ 5%) it is even higher in the frail elderly nursing home population (~ 7-10%). Cognitive impairment, or dementia often accompanies PD in patients over the age of 70. We refer to these cognitive impairments as Parkinson’s Disease Dementia (PDD). A full 75% of PD patients beyond the age of 70 years develop this dementia after 8 years from the disease onset. This extraordinary prevalence is many times greater than that found in age-matched control samples of non-PD patients.

PD is also thought to be closely related to Essential Tremor (ET). There is an increased prevalence of PD for patients previously diagnosed with ET. At the current time the etiology of ET remains a mystery.

We also examine the prevalence of two major types of genetic abnormalities. The first has been characterized in approximately 33% of Ashkenazi Jews with PD and is also identical to the defect found in Gaucher’s disease. The second is the class of mutations associated with Parkinson’s Disease and have been associated with a relatively high expression of familial PD.

Study Objectives

The primary objectives of this study were and are:

1. To further define the relationship of motor and cognitive impairments in PDD.
2. To further define the relationship of motor and cognitive impairments in ET, ET with Dementia, and in comparison to PD and PDD.
3. To further study the prevalence of two major types of genetic abnormalities. The first is the heterozygous defect which is identical to the defect found in carriers of the Gaucher’s genetic defect. The second is the class of mutations associated with Parkin. This is being done with our collaborators at the Mount Sinai Department of Genetics and Genomic Sciences.
4. To further study the post-mortem neuropathological correlates from study subjects who have donated their brains, independent of participation in this study, as part of the JHH Anatomical Tissue Gift Program. This is being done with our collaborators at the Mount Sinai Department of Neuropathology.
Method

Individuals are recruited for study through the JHL Tissue Donation Program which, through the generous donation of family members, consists of 522 brains. Thirteen percent of these brains have been diagnosed post-mortem with Parkinson’s disease.

Another source of recruitment is via the Movement Disorders Clinic. Residents attending the clinic are seen by a neurologist affiliated with the Movement Disorders Center at the Mount Sinai School of Medicine. These clinics are held monthly at all three campuses and at this time we have enrolled over 121 residents who have been studied longitudinally. In addition, 764 residents have been studied as part of other longitudinal studies to examine the relationship between cognition and motor impairment in the nursing home long-term care population.

We have also examined a subset of our clinical cases with either familial PD or Essential Tremor. These residents and family members have been enrolled into a genetics study examining the prevalence of the Gaucher genetic defect and Parkin Mutations.

Select Findings to Date

Neuropathological Studies (Selected)

1. Parkinson’s Disease Dementia (PDD): The presence of Lewy bodies (a protein mass that displaces normal cell components in nerve cells in the brain) is currently viewed as central to the presence of PDD when Alzheimer’s disease or vascular disease are not present. In a study of 16 brains we observed that 19% did not exhibit the expected distribution of Lewy bodies to explain the presence of dementia suggesting a different etiology for dementia in PDD.

2. Depression in PD: While depression is observed in 30%-40% of PD patients the origin is still not known. We examined multiple brain sites in 11 individuals diagnosed with clinical depression during their lifespan as compared to 9 subjects without a history of depression. We observed greater pathology in the depressed patients brains in the locus coeruleus and the dorsal vagus nerve. These regions are considered responsible for the production of hormones called catecholamines as contrasted to the serotonergic hormones thought to be related to the presence of depression caused by physiological changes associated with other diseases.

Resident Studies (Selected)

1. Withdrawal of PD Drugs in Advanced Parkinsonism: We withdrew PD related medications (Sinemet) from 11 residents with both advanced Parkinsonism and dementia who seemed likely not to be benefiting from the medication.. We observed no significant changes in cognitive, behavioral,
and motor function after withdrawal and believe that for these patients it may be beneficial to withdraw these medications.

2. Prevalence of PD/ET: We conducted a prevalence study of our nursing home residents and observed 21% of residents have a movement disorder. Of these residents Parkinsonism (7.1%) and Essential Tremor (8.8%) were the most prevalent.

3. Dementia Screening: We assessed the accuracy of items on the Mini-Mental State Examination to differentiate frail elderly with dementia as compared to those without dementia. In and examination of 350 residents we observed that 2 Orientation items were as accurate as the entire 20 item instrument.

4. Cambridge Cognitive Examination (CAMCOG): We assessed the use of the CAMCOG in 50 residents to determine the ability of the instrument to detect deficits in specific cognitive domains in our population. We found that the total CAMCOG score was lower than seen in previously reported normative data with the Control group having the highest score (80). This means that within our population individuals without dementia show greater overall deficits in cognition via CAMCOG testing. This was reflected by scores for Remote Memory, Abstract Thinking, and Perception related test items which failed to differentiate individuals with and without dementia. This highlights both the sensitivity of the CAMCOG test and the presence of subtle cognitive impairment in many otherwise “normal” appearing frail elderly persons.

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Funded by: Leir Charitable Foundations

Project Period: 2001-2009

Publications


Presentations
1) A Diminished role for the Lewy Body in Parkinson’s Disease Dementia. American Medical Directors Association Annual Meeting 2008, Salt Lake City, Utah.

2) Glucocerebrosidase (GBA) Gene Mutations are an Important Risk Factor for Lewy Body Inclusions n Alzheimer’s Disease patients of Ashkenazi Jewish Ancestry. 12th International meeting of the Parkinson’s Disease and Movement Disorder Society;2008 Salt Lake City, Utah.


5) Optimizing Clinical Outcomes in Residents with Parkinson’s Disease. American Medical Directors Association annual symposium in Dallas, Texas March 2006.

6) Parkinson’s Disease Dementia as a distinct neurobiological entity: insights from postmortem human brains. American Medical Directors Association annual symposium in Dallas, Texas March 2006.

7) A Memory Intervention for LTC Residents at Risk for Dementia, American Medical Directors Association, 29th Annual Symposium, Dallas, TX, March 2006.

8) Parkinson’s Disease and Movement Disorders: New Approaches to Assessment and Treatment, American Medical Directors Association, 28th Annual Symposium, New Orleans, LA, March 2005.

Updated: July 2009