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Presymptomatic Parkinson's disease: The Arizona experience

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SUMMARY

There is a growing interest in presymptomatic diagnosis of Parkinson's disease (PD), but the best and most practical method to screen and confirm asymptomatic individuals for PD needs further study. The Banner-Sun Health Brain and Body Donation program in Sun City, Arizona has studied primarily PD and Alzheimer's disease. Enrollees receive annual prospective standardized evaluation that includes clinical, biomarker testing, and at autopsy, neuropathological examination is performed followed by a consensus conference that determines final diagnosis. Since numerous Controls receive these assessments, these subjects become an excellent cohort to study presymptomatic PD. We found that Controls with partial diagnostic criteria for PD (1 of either rest tremor or bradykinesia) had a 6.6 relative risk for eventually developing full diagnostic criteria for PD. Neuropathologic examination has uncovered cases of "incidental Lewy body disease" (ILBD). We have shown that ILBD cases during life demonstrated no significant differences in clinical assessment versus similarly assessed controls. However, electrophysiological assessment showed subclinical low frequency rest discharges in some ILBD cases. Electroencephalography spectral frequency of ILBD cases was lower than for controls but not as low as for PD cases. The longitudinal assessments of this brain bank offer significant opportunities for the study of presymptomatic PD.

1. Introduction

There is growing interest in presymptomatic Parkinson's disease (PD) and the neurodegeneration that correlates with it [1,2]. It is possible that this "presymptomatic stage" offs a opportunity to administer therapy to delay or prevent PD symptoms [3,4]. As significant dopamine neuronal degeneration has already occurred by the time that Parkinson's disease (PD) has been diagnosed, finding clinical and non-clinical biomarkers that would reliably predict the eventual development of clinically probable PD are needed. The Banner Health-Sun Health Research Institute (SHRI) Brain and Body donation program resides in Sun City, Arizona. The research of PD within this program represents collaboration between SHRI and Mayo Clinic Arizona investigators. The purpose of this article is to provide some background of the tremendous potential that this program has to study PD, and to give some research highlights of this program with regard to presymptomatic PD research.

2. Banner Health-SHRI Brain and Body Donation Program

The SHRI was established in 1986. The focus of the Institute's scientific work has been neurodegenerative diseases, primarily PD and Alzheimer's disease (AD) [5]. The SHRI is also a member of the Arizona Alzheimer's Disease Consortium that has been a National Institute on Aging Alzheimer's Disease Core Center (ADCC) since 2001. The PD research program has received support from a number of sources including Banner-SHRI, Mayo Clinic, and Arizona State sources. Major support has been received from the Michael J Fox foundation for PD research. Recently, funding through a U24 resource grant has been awarded to the PD research program at SHRI.

The Brain Donation Program has been in existence for greater than 20 years with over 1500 donors enrolled (1.9% of the current combined populations of the surrounding retirement communities of Sun City, Sun City West and Sun City Grand. Of these, more than 900 donors have expired and their brains have been collected and stored. Donors have all volunteered specifically for the program and are highly motivated, with an annual drop-out rate of only 1.8%. All enrolled subjects or legal representatives sign an IRB-approved consent form allowing both clinical assessments during life and brain and bodily organ donation after death. A major strength of the Brain Donation Program has been the large number of donors who can serve as a control population. The assessment given to each subject is extensive and includes neurologic examination, movement disorders exam, and a refined neuropsychologic test battery. All assessments are prospective, standardized, and repeated in a regular longitudinal fashion until death. The standard Brain Donation Program (BDP) Assessment includes the extensive pre-mortem evaluation and a clinico-pathologic diagnosis that is determined by consensus conference.

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Table 1
Neurology assessment for Brain Donation Program enrollees

Component	Purpose/Function Tested
Subjective Historical Enquiry	Subjective symptoms, memory
Mental Status Examination	Gross cognitive and emotional
Neurologic Examination	Objective signs of abnormality
Folstein Mini Mental Status Examination (Folstein et al., 1975 [6])	Global cognitive function
Global Deterioration Scale (Reisberg et al., 1988 [7])	Level of independent function
Functional Assessment Staging (Reisberg,1988 [8])	Level of independent function to severe disability
Clinical Dementia Rating Scale (Morris,1993 [9])	Global function
Smell Test (UPSIT)	Smell function
Sleep Questionnaire	Screen for sleep problems
Autonomic Questionnaire	Screen for autonomic problems

Major items of the assessment are given in Tables 1–3 [6–10]. PD subjects are assessed annually by clinical examination as they currently are in the BDP. Control subjects are currently assessed every year and a half.

The standard assessment also involves the presence of a collateral informant. Informants will be asked a standard set of questions that include questions about memory impairment, depression, functional impairment, and neuropsychiatric features. The informant will typically be the spouse or adult child. The expectation is that the informant has exposure to the subject 4 hours per day at least three days per week. The information from the informant is used to determine functional status which is incorporated into assessing whether dementia is present or not.

By using all available information from the pre-mortem evaluations and autopsy results, a consensus conference among neurologists and neuropsychologist determines diagnosis and the presence or absence of dementia is determined by DSM-IV and Movement Disorder Society criteria. Clinically suspected Control subjects must also be determined to have no neurological disorder, no dementia, and have autopsy confirmation consistent with control status.

Table 2
Neuropsychology test battery for Brain Donation Program enrollees

Test	Modality Tested
WAIS-III Digits Forward and Backward	Attention
Rey Auditory Verbal Learning Test	Verbal learning and memory
Controlled Oral Word Association	Oral language generative fluency
Category Fluency	Oral language generative fluency/executive
Clock Drawing	Visuospatial/motor
Judgement of Line Orientation	Visuospatial/nonmotor
Trails Part A	Visuospatial processing speed
Trails Part B	Visuospatial processing speed/executive
STROOP	Frontal/Executive
Geriatric Depression Scale	Depression
Hamilton Depression Scale	Depression
Mattis Dementia Rating Scale	Severe cognitive impairment[a]
Neuropsychiatric Inventory (NPI-Q)	Neuropsychiatric symptoms

[a] For subjects who meet floor level on other global assessment tests.

Table 3
Movement disorders screening assessment

Component	Purpose/Function Tested
Directed Neurologic Examination	Movement Disorder detection
Tapping Test	Motor speed and coordination
Purdue Pegboard Test	Motor speed and coordination
Unified PD Rating Scale (UPDRS)	Degree of parkinsonism in PD
Hoehn and Yahr Staging (H&Y)	Functional staging of motor ability

3. Studies of presymptomatic PD at SHRI

We have examined our longitudinal data in a variety of ways to study presymptomatic PD. The diagnosis of PD requires finding 2/3 clinical signs of bradykinesia, rest tremor, and rigidity. We analyzed whether individuals with just rest tremor or bradykinesia (one cardinal PD sign) were more likely than Controls without such a sign to have motor testing abnormalities and/or develop clinically probable PD at 5 years of follow-up [11]. Using a total of 841 subjects in a brain donor program that had undergone 2,068 examinations by a movement disorders specialist since 1997 with serial examinations of 553 of these subjects, mean follow-up was 3.5 yrs. Initial examination categorized 336 subjects as controls, 85 as clinically possible PD (PPD, either rest tremor or bradykinesia), and 127 as clinically probable PD (DPD, 2/3 cardinal signs). Motor testing differed between groups (DPD < PPD < Control). Of those subjects having at least 5 yrs follow-up, 5/79 (6.3%) of the Controls became DPD, while 13/33 (39.3%) of the PPD became DPD. This is a relative risk = 6.3 for developing DPD if initially PPD. The motor testing did not add to the predictive value of the battery. These data can be used to develop a neuroprotective trial to reduce the conversion from PPD to DPD. If the placebo group conversion rate at 5 yrs is 39%, and the active drug treatment group reduces the incidence of converting by half, to 20%, then a sample of 90 clinically possible PD patients per group followed for 5 yrs would have 80% power to detect this difference. This study established: (1) rate of development of clinically probable PD over time, and that (2) clinically possible PD cases can be utilized for neuroprotection trials to slow progression to clinically probable PD.

The Lewy body is the pathological hallmark of Parkinson's disease (PD) and dementia with Lewy bodies (DLB). Lewy bodies have been reported in 10–30% of undiagnosed elderly persons [12,13]. "Incidental Lewy Body Disease" (ILBD) refers to the presence of Lewy bodies at autopsy in the absence of a clinical diagnosis. Our group recently found decreased striatal tyrosine hydroxylase (TH) in subjects with ILBD, and this finding was interpreted to possibly suggest that ILBD represents preclinical PD and DLB [14]. Other investigators have confirmed that other striatal dopamine markers are depleted in ILBD to levels intermediate between those of PD and control [15,16]. Thus, these findings and those of other groups suggest that such "incidental Lewy bodies" may be a precursor to the eventual clinical onset of PD or Dementia with Lewy bodies (DLB) [17–19].