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Cardiac sympathetic denervation predicts PD in at-risk individuals

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Abstract

Introduction: By the time a person develops the motor manifestations of Parkinson's disease (PD), substantial loss of nigrostriatal dopamine neurons has already occurred. There is great interest in identifying biomarkers that can detect pre-clinical PD. Braak's neuropathological staging concept imputes early autonomic involvement. Here we report results from a small prospective cohort study about the utility of neuroimaging evidence of cardiac sympathetic denervation in predicting PD among individuals with multiple PD risk factors.

Methods: Subjects provided information about family history of PD, olfactory dysfunction, dream enactment behavior, and orthostatic hypotension at a protocol-specific website. From this pool, 27 people with at least 3 risk factors confirmed underwent cardiac ¹⁸F-dopamine positron emission tomographic scanning and were followed for at least 3 years. Interventricular septal and left ventricular free wall concentrations of ¹⁸F-dopamine-derived radioactivity were measured.

Results: Of the 27 subjects, 4 were diagnosed with PD within the 3-year follow-up period (Pre-Clinical PD group); 23 risk-matched (mean 3.2 risk factors) subjects remained disease-free (No-PD group). Compared to the No-PD group, the Pre-Clinical PD group had lower initial values for septal and free wall concentrations of ¹⁸F-dopamine-derived radioactivity ($p = 0.0248, 0.0129$).

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Author contributions

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Conflicts of interest

The authors report no conflicts of interest.

All 4 Pre-Clinical PD subjects had evidence of decreased cardiac sympathetic innervation in the interventricular septum or left ventricular free wall, in contrast with 3 of 23 (13%) No-PD subjects ($p = 0.0020$ by Fisher's exact test).

Conclusion: People with multiple PD risk factors and diagnosed with PD within 3 years have evidence of antecedent cardiac sympathetic denervation. The findings fit with Braak's staging concept.

Keywords

Parkinson's disease; Sympathetic nervous system; Fluorodopamine; Biomarkers

The movement disorder in Parkinson's disease (PD) reflects depletion of the catecholamine, dopamine, in the nigrostriatal system. According to Braak's staging concept, nigral neuropathological involvement in PD occurs in Stage 3 of 6 stages [1]. There is great interest in identifying biomarkers of PD at an earlier stage; these could help elucidate pathogenetic mechanisms and help test possible disease-modifying strategies.

Braak's concept imputes early autonomic involvement. In particular, cardiac sympathetic neurodegeneration seems to occur early in the disease process. Individuals with incidental Lewy body disease, thought to be a precursor of symptomatic PD, have decreased epicardial immunoreactive tyrosine hydroxylase, a marker of cardiac sympathetic denervation [2]. A case report noted neuroimaging evidence of cardiac sympathetic denervation 4 years before the development of motor signs of PD [3]; however, no study has assessed prospectively whether cardiac sympathetic neuroimaging predicts PD in at-risk individuals. We report initial results from such a study, involving individuals with multiple PD risk factors who underwent ^{18}F -dopamine positron emission scanning and then were followed for at least 3 years.

1. Methods

The prospective cohort "PDRisk" study in the intramural research program of the National Institute of Neurological Disorders and Stroke (NINDS) is testing whether at-risk individuals with biomarkers of catecholamine deficiency have pre-clinical PD. Risk factors in the study are genetics, olfactory dysfunction, symptoms of rapid eye movement behavior disorder (RBD), and symptoms of orthostatic hypotension (OH). These were chosen based on epidemiologic evidence that they can be found early in PD and can precede motor signs by several years [4–6]. At least 3 of the 4 risk factors are required for accrual into the study, to enrich the population and minimize radioactivity exposure to research subjects.

1.1. Protocol approvals, registrations, and patient consents

Subjects in this study gave written informed consent to participate in intramural protocols approved by the NINDS institutional review board (IRB). Consent for the PDRisk study was in two forms—electronic at a protocol-specific, IRB-approved website and in writing at the time of evaluation at the Clinical Center of the National Institutes of Health (NIH).

1.2. Inclusion criteria

There were 4 categories of risk—genetic, olfactory, symptoms of RBD, and OH. With respect to genetics, a positive family history (one immediate or more than one non-immediate family member with PD) or positive genetic testing (e.g., LRRK2, alpha-synuclein, glucocerebrosidase) satisfied this criterion. Olfactory dysfunction reported at the protocol-specific website satisfied the criterion. To satisfy the RBD risk factor criterion, the individual or member of the individual's household must have reported that the individual had movements of the body or limbs associated with dreaming and at least one of the following: potentially harmful sleep behavior, dreams that appeared to be acted out, and sleep behavior that disrupted sleep continuity. To satisfy the OH risk factor criterion, the individual must have reported symptoms of OH or having OH as defined by consensus criteria.

1.3. Exclusion criteria

People younger than 18 years old or older than 70 years old were excluded. A candidate subject was excluded if there was a disqualifying condition or clinical considerations required continued treatment with a drug likely to interfere with the scientific results. Examples of disqualifying conditions were insulin-dependent diabetes, hepatic or renal failure, symptomatic congestive heart failure, severe anemia, psychosis, ventricular arrhythmias, and symptomatic coronary heart disease.

1.4. Study design

The primary outcome measure was a diagnosis of PD by a neurologist who was blinded to the results of the catecholaminergic biomarkers testing. Data collection has been ongoing since 2009.

Recruitment was by advertisement using a Google ad referring to a protocol-specific, IRB-approved webpage that complied with the Privacy Act. Candidate participants who were flagged as reporting at least 3 risk factors were interviewed by phone by a Research Nurse, to confirm the self-reported information and select subjects for on-site screening.

The screening examination at the NIH Clinical Center was to obtain consent for further participation in the study, verify at least 3 risk factors, and perform clinical and laboratory tests (e.g., the University of Pennsylvania Smell Identification Test and autonomic function tests described below). Subjects with at least 3 confirmed risk factors underwent inpatient biomarkers testing.

For follow-up testing subjects were re-evaluated at about 1.5- year intervals, for neurological examinations and imaging reassessments. Participants who started on exclusionary drugs after enrollment were not brought back for follow-up inpatient testing; however, they could be contacted by phone, mail, or secure e-mail, to learn of their clinical status.

PD was diagnosed according to accepted clinical criteria such as bradykinesia, rigidity, resting tremor, and imbalance.

1.5. Identification of OH

Each subject was evaluated in a dedicated patient testing room in the NIH Clinical Center. After at least 15 min with the subject at supine rest, the subject was tilted head-up at 90° for 5 min. OH was defined as a decrease in systolic blood pressure of at least 20 mmHg or in diastolic pressure of at least 10 mmHg between lying supine and head-up tilting for at least 3 min.

1.6. Cardiac sympathetic neuroimaging

Subjects underwent cardiac sympathetic neuroimaging by ¹⁸F-DA positron emission tomographic scanning, as described previously [7]. Briefly, interventricular septal and free wall ¹⁸F-DA-derived radioactivity was recorded for the 5-min frame with a mid-point about 8 min after initiation of the 3-min infusion of 1 mCi of the tracer.

1.7. Comparison groups

A total of 12 controls without PD risk factors who were evaluated at the NIH had data for the neuroimaging biomarkers (mean age 62 years old, age range 44–78 years old, 9 males). Inpatient biomarkers data were also included from 16 patients with established PD (mean age 61.1 years old, age range 42–78 years old, 11 males) studied under other protocols.

1.8. Study size, data analysis, and statistics

To determine the minimum required numbers of subjects, we used a log-rank test for the interval between biomarkers testing and diagnosis of PD and estimated that among individuals at risk of PD and who had abnormal catecholaminergic biomarkers, 80% would develop PD by 7.5 years of follow-up; and that among at-risk participants without abnormal biomarkers, 20% would develop PD during follow-up. Considering the possibility of dropouts, at an alpha value of 0.05 and beta value of 0.20, follow-up from a group of 26 subjects with complete baseline biomarkers data would be sufficient.

An interim analysis was done after 3 years of follow-up, for calculation of the positive predictive value of the biomarkers (Phase 1). The negative predictive value of absent biomarkers will be calculated at the end of the study (7.5 years of follow-up).

The investigators carrying out the image analyses and the neurologist diagnosing PD were blinded as to the clinical risk factors and other biomarkers.

For the Pre-Clinical PD and No-PD groups, receiver operating characteristic (ROC) curve analyses were performed to evaluate the accuracy of prediction. A method based on ROC analysis and the and points on the minimum distance between the point (0,1), the perfect predictor, and points on the ROC curve was used to select the optimal cutoff thresholds for binary predictions. The dichotomized biomarkers data based on the cutoff values were then analyzed by Fisher's exact test, with quantification of sensitivity and specificity.

2. Results

2.1. On-site screening

A total of 31 accrued participants had at least 3 of the 4 risk factors confirmed upon on-site screening at the NIH Clinical Center. Of these, 3 reported having been diagnosed with PD between the time of registration at the protocol-specific website and the time of on-site screening and were excluded from further participation. Therefore, 28 at-risk subjects had inpatient biomarkers testing. One subject was withdrawn because of his being on an anti-coagulant, which was exclusionary. None of the participants had an identified mutation of the alpha-synuclein, leucine-rich repeat kinase 2, or glucocerebrosidase genes.

Of the 27 remaining subjects, 4 developed PD within 3 years of follow-up testing (Pre-Clinical PD group; mean age 60.4 years old, age range 53–70 years old, 3 males). A total of 23 at-risk subjects had inpatient biomarkers data, were followed for at least 3 years, and did not have PD diagnosed during that time (No-PD group; mean age 55.2 years old, age range 40–68 years old). The mean SD of the follow-up time in the No PD group was 4.2 1.4 years. By the time of diagnosis, all 4 subjects with pre-clinical PD had low putamen/occipital cortex ratios of ^{18}F -DOPA-derived radioactivity, consistent with nigrostriatal dopaminergic neurodegeneration [7]. Two developed prominent dementia suggestive of dementia with Lewy bodies (DLB), with visual hallucinations and fluctuating mentation. In both patients, symptoms of DLB developed before their PD diagnosis, and in both, parkinsonism was relatively mild, and the main problems were orthostatic intolerance and cognitive dysfunction.

The No PD group did not differ from the controls in terms of septal or free wall ^{18}F -DA-derived radioactivity ($p = 0.50$, 0.44 by independent means t-tests).

2.2. Established PD vs. control groups

As expected, mean (SEM) values for ^{18}F -dopamine-derived radioactivity were lower in the septum and free wall in the group with established PD (6142 836 and 5377 812 nCi/kg/cc-mCi) than in the Control group (9377 503 and 9322 633 nCi/kg/cc-mCi; unequal variance $t = 3.31$, $p = 0.0027$, and $t = 3.83$, $p = 0.0007$).

2.3. Dichotomized positive biomarkers by cutoff values

Areas under the ROC curves were 0.880 (95% confidence interval 0.703–1.00) for the septum and 0.870 (0.723–1.00) for the free wall. The chosen cutoff value for septal ^{18}F -dopamine-derived radioactivity was 6000 nCi/kg/cc-mCi and for free wall radioactivity 5600 nCi/kg/cc-mCi.

Based on the dichotomized biomarkers, among the at-risk subjects, 3 of the 4 in the Pre-Clinical PD group had low septal radioactivity (75%), compared 3 of the 23 in the No-PD group (13%; $p = 0.0248$). In the Pre-Clinical PD group, 3 had low free wall radioactivity (75%), compared to 2 of 23 in the No-PD group (7%; $p = 0.0128$). All 4 subjects in the Pre-Clinical PD group had low septal or free wall radioactivity (100%), compared to 3 of the 23

in the No-PD group (13%; $p = 0.0020$ by Fisher's exact test). The sensitivity of low septal or free wall radioactivity was therefore 100% at a specificity of 87%.

3. Discussion

The data from this small prospective cohort study show that among highly selected individuals with multiple PD risk factors (at least 3 of the following: positive family history, olfactory dysfunction, symptoms of RBD, symptoms of OH), those with biomarkers of cardiac sympathetic denervation in the interventricular septum, free wall, or both have pre-clinical PD.

The PDRisk cohort had a $4/27 = 15\%$ incidence of PD over 3 years, compared to an estimated less than 1% in the general adult population [8]. Having multiple risk factors therefore increases the likelihood of developing PD [9]. The key new finding in the present study is that in the setting of multiple PD risk factors, having biomarkers of cardiac sympathetic denervation increases this likelihood substantially. ^{18}F -Dopamine cardiac scanning is currently done routinely only at the NIH Clinical Center. On the other hand, ^{123}I -metaiodobenzylguanidine scanning is widely available, and recent cross-sectional studies suggest that abnormal results by this modality can identify PD [10].

Clinical researchers are increasingly questioning whether PD should be defined solely by motor features because of sometimes prominent non motor aspects such as cognitive dysfunction. The results from the present study add to the conversation, because 2 of the 4 subjects in the Pre-Clinical PD group developed prominent dementia with features indicating diffuse Lewy body involvement (visual hallucinations, fluctuating cognitive status). According to consensus definitions, these subjects had DLB, because dementia became manifest before or less than one year after the onset of parkinsonism. Including OH among the risk factors may have biased toward obtaining evidence of cardiac noradrenergic denervation, because this finding is universal in PD + OH [11]. Since the non-motor aspects of PD tend to cluster together—especially dementia with cardiac sympathetic denervation [12], it is unclear to what extent cardiac sympathetic denervation is predictive of PD vs. DLB.

3.1. Study limitations

The PDRisk study involves long-term, inpatient follow-up evaluations of a relatively small number of highly selected, intensively studied participants. These aspects enabled sufficient statistical power to test the main hypothesis but at the expense of limited generalizability. In particular, since all the PDRisk subjects reported here had a highly unusual combination of multiple risk factors, we do not know how the results would apply in people with fewer or different risk factors. The study is being continued, to determine whether conversion from negative to positive biomarkers occurs before the motor onset of PD.

From the risk factors and biomarkers used in the study, we may have identified the “diffuse malignant” form of PD, as reported by Postuma's group [13].

4. Conclusions

Consistent with the Braak staging scheme, neuroimaging evidence of cardiac sympathetic neuroimaging seems to identify efficiently those at-risk individuals who actually develop clinical PD within 3 years of follow-up. Biomarkers of cardiac noradrenergic neurodegeneration might prove useful for selection of candidates for treatment and prevention trials.

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References

- [1]. Braak H, Ghebremedhin E, Rub U, Bratzke H, Del Tredici K, Stages in the development of Parkinson's disease-related pathology, *Cell Tissue Res.* 318 (2004) 121–134. [PubMed: 15338272]
- [2]. Orimo S, Takahashi A, Uchihara T, Mori F, Kakita A, Wakabayashi K, Takahashi H, Degeneration of cardiac sympathetic nerve begins in the early disease process of Parkinson's disease, *Brain pathol. Zurich, Switz* 17 (1) (2007) 24–30.
- [3]. Goldstein DS, Sharabi Y, Karp BI, Benth O, Saleem A, Pacak K, Eisenhofer G, Cardiac sympathetic denervation preceding motor signs in Parkinson disease, *Clin. Auton. Res* 17 (2) (2007) 118–121. [PubMed: 17334896]
- [4]. Schapira AH, Jenner P, Etiology and pathogenesis of Parkinson's disease, *Mov. Disord. official J. Mov. Disord. Soc* 26 (6) (2011) 1049–1055.
- [5]. Kim JS, Lee SH, Oh YS, Park JW, An JY, Park SK, Han SR, Lee KS, Cardiovascular autonomic dysfunction in mild and advanced Parkinson's disease, *J. Mov. Disord* 9 (2) (2016 5) 97–103. [PubMed: 27020456]
- [6]. Lee H, Cho YW, Kim HA, The severity and pattern of autonomic dysfunction in idiopathic rapid eye movement sleep behavior disorder, *Mov. Disord* 30 (13) (2015) 1843–1848. [PubMed: 26381053]
- [7]. Goldstein DS, Holmes C, Benth O, Sato T, Moak J, Sharabi Y, Imrich R, Conant S, Eldadah BA, Biomarkers to detect central dopamine deficiency and distinguish Parkinson disease from multiple system atrophy, *Park. Relat. Disord* 14 (8) (2008) 600–607.
- [8]. Elbaz A, Bower JH, Maraganore DM, McDonnell SK, Peterson BJ, Ahlskog JE, Schaid DJ, Rocca WA, Risk tables for parkinsonism and Parkinson's disease, *J. Clin. Epidemiol* 55 (1) (2002) 25–31. [PubMed: 11781119]
- [9]. Postuma RB, Gagnon JF, Bertrand JA, Genier Marchand D, Montplaisir JY, Parkinson risk in idiopathic REM sleep behavior disorder: preparing for neuroprotective trials, *Neurology* 84 (11) (2015) 1104–1113. [PubMed: 25681454]
- [10]. Yoshii F, Ryo M, Baba Y, Koide T, Hashimoto J, Combined use of dopamine transporter imaging (DAT-SPECT) and 123I-metaiodobenzylguanidine (MIBG) myocardial scintigraphy for diagnosing Parkinson's disease, *J. Neurol. Sci* 375 (2017) 80–85. [PubMed: 28320195]
- [11]. Goldstein DS, Dysautonomia in Parkinson disease, *Compr. Physiol.* 4 (2) (2014) 805–826.
- [12]. Orimo S, Amino T, Takahashi A, Kojo T, Uchihara T, Mori F, Wakabayashi K, Takahashi H, Cardiac sympathetic denervation in Lewy body disease, *Park. Relat. Disord* 12 (Suppl 2) (2006) S99–S105.
- [13]. Fereshtehnejad SM, Romenets SR, Anang JB, Latreille V, Gagnon JF, Postuma RB, New clinical subtypes of Parkinson disease and their longitudinal progression: a prospective cohort comparison with other phenotypes, *JAMA Neurol.* 72 (8) (2015) 863–873. [PubMed: 26076039]