Protocol Title: ***Characterization of Motor Function and Potential Transition States to Parkinson's Disease in LRRK2 Mutation Carriers and Controls***

Date and Version: **28 March 2016- Version 1.0**

Sponsor: **Michael J Fox Foundation**

Investigators: **Anat Mirelman, PhD, Nir Giladi, MD, and Jeffrey Hausdorff, PhD**
Tel Aviv Medical Center, Israel

PROTOCOL APPROVAL

Characterization of Motor Function and Potential Transition States to Parkinson's Disease in LRRK2 mutation Carriers and Controls

Date and Version: 28 March 2016

Version 1.0

Kenneth Marek, MD Date
Principal Investigator

Karl Kieburtz, MD, MPH Date
Clinical Core

Todd Sherer, PhD Date
Michael J Fox Foundation (Sponsor)

Anat Mirelman, PhD Date
Tel Aviv Medical Center, Israel

INVESTIGATOR'S AGREEMENT TO PROTOCOL

Protocol: Characterization of Motor Function and Potential Transition States to Parkinson's Disease in LRRK2 mutation Carriers and Controls

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I agree to conduct the study according to this protocol and to comply with its obligations, subject to ethical and safety considerations and all applicable regulations (ICH, CFR).

I shall not disclose the confidential information contained in this protocol or any results obtained from the study, without written authorization from PPMI.

Principal Investigator:

_____ _____

Printed Name Date

_____

Signature

PROTOCOL SYNOPSIS

Title of Study: Characterization of Motor Function and Potential Transition States to Parkinson's Disease in LRRK2 mutation Carriers and Controls
Funding: Michael J Fox Foundation
Number of Subjects: 100
Study Centers: 6, with additional sites possible
Objectives: Obtain longitudinal motor function data at a subset of PPMI sites.
Primary Outcome Measure: The primary outcome measure is gait variability during challenging walks. Assessment will include standing 30 seconds with feet together and eyes open and 30 seconds with eyes closed to measure sway (center of mass displacement under usual and challenging conditions). In addition, subjects will be asked to walk under 3 different walking conditions each of 1 minute; 1) preferred speed walking, 2) dual task; walking while serially subtracting 7's from a predefined 3 digit number; 3) fast walking speed.
Significance/Relevance: Gait disturbances play a major role in the motor manifestation of PD. Traditional assessments aimed at measuring motor deficits, including the UPDRS, do not identify subtle differences in individuals at risk for PD, while quantitative measures have shown promise in this. Therefore, more sensitive tests of motor function are needed to increase the likelihood of identifying pre-diagnosis motor changes. Quantitative measures of gait and mobility should provide a means for assessing pre-diagnosis changes.
Study population: Recently diagnosed patients with PD (up to 3 years from diagnosis) and asymptomatic carriers and non-carriers of the G2019S mutation will be eligible to participate.
Study Design: This protocol is a companion to the Parkinson's Progression Markers Initiative (PPMI)

protocol. All demographic and clinical data will be collected as part of PPMI and linked through a common subject identifier.

Participating subjects will complete 2 gait assessments at yearly intervals. Subjects consenting to the gait assessment study will consent and complete their first assessment at an annual visit. The second assessment will be conducted the next annual visit.

Device:

The system includes 3 lightweight wireless wearable sensors containing 3 axial accelerometers, gyroscopes and magnetometers (Opal, APDM Ltd.). The system measures acceleration of movement in 3 orthogonal axes as a function of time. The recording unit is small, lightweight and housed in a custom made Velcro-belt. The sensors will be worn on both wrists and on the lower back of the participants during all gait measurements to quantify temporal measures such as stride time, gait variability, step symmetry, axial angular movement in three planes, and magnitude and symmetry of arm swing during each of the walks.

Assessments:

Assessment will include standing 30 seconds with feet together and eyes open and 30 seconds with eyes closed to measure sway (center of mass displacement under usual and challenging conditions). In addition, subjects will be asked to walk under 3 different walking conditions each of 1 minute; 1) preferred speed walking, 2) dual task; walking while serially subtracting 7's from a predefined 3 digit number; 3) fast walking speed.

Total assessment time including set-up: About 20 minutes

Data Analysis:

Data will be saved onto a designated computer at each site and later transferred to a central database for further analysis at the Center for the study of Movement, Cognition and Mobility at the Tel Aviv Medical Center. Processed data will be uploaded to the PPMI LONI website as open access data.

Introduction

Motor symptoms are the hallmark of Parkinson's disease (PD). It is, therefore, understandable that widely used scales like the Hoehn and Yahr staging track disease severity based on the patient's motor function. Since PD is likely a long, neurodegenerative process that begins many years prior to diagnosis[1, 2], we[3]and others[4, 5] reason that subtle motor changes are present even years prior to the diagnosis and the full blown manifestation of PD motor symptoms. Quantitative measures of gait and mobility should provide a means for assessing these pre-diagnosis changes. Indeed, as detailed further below, our preliminary work supports this intriguing idea.

Currently, the Unified Parkinson Disease Rating Scale (UPDRS) motor sub-score is the only measure of motor function in PPMI. While the motor part of the UPDRS is widely used in studies in PD and for diagnosis purposes, it is generally applied as a progression marker, and likely cannot serve as a predictive measure in pre-clinical disease[6, 7]. In a study of elderly *G2019S* carriers, baseline motor UPDRS did not predict conversion to PD[8]. Similarly, in our cohort of pre-symptomatic *G2019S* carriers and non-carriers[3], both groups had near zero scores on the motor part of the UPDRS and this test could not identify subtle differences in individuals at risk, while quantitative measures did. Thus, we reason that more sensitive tests of motor function are needed to increase the likelihood of identifying pre-diagnosis motor changes.

Background

Gait disturbances play a major role in the motor manifestation of PD. Alterations in the gait pattern that are frequently observed in patients with PD include decreased velocity, small shuffling steps, reduced arm swing, shortened strides, and loss of consistency in one's ability to produce a steady gait rhythm which in turn produces stride-to-stride variability [10-13]. It has been suggested that impairment of internal clocking mechanisms disrupts the normal motor programming needed to perform automatic, sequential movements[10, 11] and leads to increased gait variability in patients with PD. Changes in gait speed and variability can already be detected in recently diagnosed, de novo patients, even before any visible or symptomatic gait disturbances are reported[10, 14]. In addition, gait variability measures respond to medication (on vs. off cycles)[15-18] and are associated with disease progression[19, 20].

Our preliminary gait data in non-manifesting *LRRK2* carriers supports the idea that motor features may be abnormal several years prior to the development of PD. We reported on the existence of subtle gait alterations in healthy asymptomatic G2019S mutation carriers during challenging tasks (fast walking and dual-task gait conditions)[3]. The non-manifesting carriers walked with significantly higher gait variability, compared to the non-carriers. Similarly, the width of the dominant frequency in the locomotion band was larger in the carriers, indicative of a less consistent, more variable walking pattern). This finding suggests an association between carrying the LRRK2 *G2019S* mutation and poorer performance in gait dynamics.

The use of quantitative objective measures during challenging conditions that utilize neural compensatory mechanisms apparently enabled the detection of subtle changes in motor function. This result has now been observed on a larger sample of carriers of *G2019S* mutation from the Gait Consortium study funded by the MJFF (n=122), confirming earlier findings and demonstrating that gait can be a sensitive measure for detection of early motor changes.

Reduced arm swing is a known clinical feature in PD that has traditionally been described in an observational manner. Arm swing in PD diminishes in amplitude and speed and inter-limb asymmetry is observed in early stages of the disease, reflecting the unilaterality of the early stages. With time, this asymmetry slowly decreases as the disease progresses. By using accelerometers, it is possible to quantify arm swing and changes in amplitude and asymmetry. In the Gait Consortium protocol, arm swing symmetry and magnitude was assessed using accelerometers placed on the wrists of the participants during the gait assessment trials. Increased arm swing asymmetry was detected in both patients with PD carriers of the LRRK2 G2019S mutation and non-manifesting carriers, compared to non-carriers ($p<0.009$). Despite similar disease duration and severity, patients with PD carriers of the G2019S mutation walked with lower arm swing amplitude and higher arm swing asymmetry ratio than PD non-carriers. These findings were consistent with higher gait variability and a higher frequency of Postural Instability Gait Difficulty (PIGD) manifestation in PD carriers, as compared to non-carriers. Interestingly, non-manifesting carriers walked with higher asymmetry ratios and worse arm swing jerk (smoothness) as compared to the non-carriers in the challenging gait conditions. The findings suggest that arm swing measures may be related to LRRK2, further indicating that quantitative evaluation of arm swing may have utility for identifying early motor changes even in prodromal PD.

Another common motor feature of PD is axial rigidity manifested by decreased movement of the trunk. At present, axial rigidity is measured using the UPDRS-III by assessing movement of the neck which may not be fully reflective or specific to be considered as an early marker. Axial movement, specifically rotation around the vertical axis, is severely diminished in PD but has not yet been described in the literature specifically because of the difficulty in assessment and quantification. Preliminary by the gait consortium has shown that axial movement can be quantified and identified even in early stages of the disease.

These encouraging findings are intriguing and demonstrate the possible existence of motor changes in the prodromal phase. Nonetheless, cross sectional information is not sufficient to conclude whether these features can truly identify potential markers of disease or phenoconversion. This information can only be attained through longitudinal studies.

Study Objectives

We believe that in order to detect early changes that may be indicative of disease, potential measures and conditions should be: 1) quantitative, as there are subtle aspects of movement which are not yet observable by visual inspection4; 2) sufficiently complex to be able to challenge compensatory mechanisms, and 3) assessed longitudinally. Therefore we propose a battery of markers that has already established itself as useful in prospective studies[4, 5], in LRRK2 cohorts [3, 9], and are ecologically valid.

We propose to perform a simple gait test annually in order to identify potential motor markers of disease in the prodromal phase. We anticipate that the data collected will provide insight into phenoconversion and motor biomarkers. This study will serve to inform on pre-clinical symptoms, progression markers, and dynamic changes of function throughout disease and potential modifiers and mediators of motor symptoms. Thus we will add a short motor assessment to PPMI for at least a sub-group of participating sites.

Participants

One hundred (100) subjects will participate in the current study. Subjects from the genetic cohort will be invited to participate. Recently diagnosed patients with PD (up to 3 years from diagnosis) and asymptomatic carriers and non-carriers of the LRRK2 G2019S mutation will be eligible to participate.

Procedures

Assessment

The gait system used includes 3 lightweight wireless wearable sensors containing 3 axial accelerometers, gyroscopes and magnetometers (Opal , APDM Ltd.). The system measures acceleration of movement in 3 orthogonal axes as a function of time. The recording unit is small, lightweight and housed in a custom made Velcro-belt. The sensors will be worn on both wrists and on the lower back of the participants during all gait measurements to quantify temporal measures such as stride time, gait variability, step symmetry, axial angular movement in three planes, and magnitude and symmetry of arm swing during each of the walks. The system is robust and data collected has been validated on large cohorts.

Assessment will include standing 30 seconds with feet together and eyes open and 30 seconds with eyes closed to measure sway (center of mass displacement under usual and challenging conditions). In addition, subjects will be asked to walk under 3 different walking conditions each of 1 minute; 1) preferred speed walking, 2) dual task; walking while serially subtracting 7's from a predefined 3 digit number; 3) fast walking speed. Total assessment time including set-up is about 20 minutes.

Schedule of Assessments

Participating subjects will complete 2 gait assessments at yearly intervals. Subjects will be asked to consent to the gait assessment study at an annual visit and complete the first assessment at that same visit. Subjects will then complete the second gait assessment at their subsequent annual visit the next year.

Subjects who withdraw from the gait assessment companion study may continue participation in PPMI; however, if a subject withdraws from the parent PPMI study, the subject must also be withdrawn from the gait assessment companion study.

Risks

Risks associated with the gait assessments include those that can normally occur during routine over ground walking. Subjects with PD who are at a high risk for falls should be accompanied by a researcher when completing the test to ensure safety.

Data recording and transfer

Subjects will retain the unique identification number assigned as part of the PPMI study. Data from gait system assessments will be saved onto a designated computer at the PPMI site and later transferred (via a secured ftp site) to a central database at TASMC for further analysis. Additional demographic information needed for the processing (i.e., age, gender, disease duration etc.) will be extracted from the PPMI database using the unique patient identification number. Data processing will be performed in the Center for the

study of Movement, Cognition and Mobility at the Tel Aviv Medical Center. Processed data will be uploaded to the PPMI website LONI as open access data.

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