PROTOCOL TITLE: Quantitative Mapping of Substantia Nigra Iron in Parkinson's Disease (Stages I-IV, REM sleep behavior disorder) and Controls

PRINCIPAL INVESTIGATOR: Dr. Alexander Shtilbans, MD, PhD, Weill Cornell Medicine

IRB Protocol #: 1711018740

ClinicalTrials.gov Identifier: NCT03675282

Current Version: September 10, 2021

Prior Version Dates:
Version September 10, 2021
Version August 4, 2021
Version May 11, 2021
Version September 9, 2019
Version February 2, 2019
Version November 28, 2018
Version October 25, 2018
Version September 26, 2018
Version June 29, 2018
Version November 9, 2017

BACKGROUND

To help the development of iron chelation as a potential therapy for Parkinson's Disease (PD), this study is designed to establish an accurate and sensitive Quantitative Susceptibility Mapping (QSM)-based Substantia Nigra (SN) iron mapping method. Furthermore, should trials of iron chelation therapy in PD prove that this intervention has clinical effectiveness, an improved method to measure SN iron concentration (such as QSM as proposed herein) could become a companion Radiological Biomarker for triage and response assessment; and potentially for dose modulation to prevent potential over-treatment. We propose a study to assess SN iron changes to test the hypothesis that the QSM based iron mapping technique is more sensitive than the current R2* method for monitoring nigral iron change in PD patients. Prooxidant iron accumulation in the substantia nigra pars compacta (SNc) in the midbrain is one possible reason for SNc vulnerable to neurodegeneration. Increased iron in SN of PD patients have been evaluated by various MRI methods to be correlated with disease severity, duration, and other patient assessments. Longitudinal studies show that iron estimated by MRI progressively increase in PD subjects but not in controls. Iron elevation can cause cell death mediated by oxidative stress. The increased iron is located within individual dopaminergic neurons in the PD SNc, which leads to the following consequences: 1) The interaction of ferrous iron (Fe(II)) with oxygen (hydrogen peroxide) readily generates highly toxic hydroxyl radicals (HO¿) via Fenton chemistry. Post mortem PD-affected brains display increased lipid peroxidation, oxidative damage to DNA, and lowered levels of the reduced form of glutathione, which all reflect oxidative stress. 2) Iron can impact the aggregation of alfa-synuclein, the major component of Lewy bodies in PD. Alfa-synuclein binds to iron, which accelerates its aggregation into fibrils and is consistent with pathological finding of enriched iron in Lewy bodies. Alfa-synuclein has also been shown to directly generate hydrogen peroxide when it aggregates and, in the presence of iron, produces toxic hydroxyl radicals. 3) The aggregation of alfa-synuclein in PD can proliferate microglia, and iron can polarize microglia to the pro-inflammatory M1 phenotype that produces cytotoxic cytokines, which is observed in the advanced dopaminergic degeneration in symptomatic PD. While noninvasive MRI is sensitive to the presence of iron that is paramagnetic, current MRI methods to quantify iron are highly problematic. A commonly used method is the signal decay rate R2*, to be precise, the decay rate of the magnitude signal along the data sampling echo time TE in the commonly used gradient echo sequence. We have found that R2* suffers from various problems including 1) dependences on imaging parameters including voxel size and field strength, 2) blooming artifacts, which are particularly strong at SNc that is near the nasal cavity air-tissue interface of strong magnetic susceptibility difference, and 3) interfering effects from cellular contents such as membranes, proteins (neuromelanin, alpha-synuclein, etc). Our investigations have lead to the physics insight to model MRI signal dependence on paramagnetic iron, which is the so called forward problem from iron to MRI signal phase or field. Accordingly, we have innovated the inverse solution from field to iron source, which is termed as quantitative susceptibility mapping (QSM). We are performing ex vivo studies to demonstrate that QSM is much more accurate that R2* for measuring

iron by comparing with elemental analysis, the gold standard. This in vivo patient project is designed to demonstrate that QSM will provide much better image quality and higher sensitivity than R2* quantitatively mapping iron in SNc.

STUDY DESIGN

Prospective, single center trial to determine whether the current R2* iron mapping method for measuring nigral iron changes in Parkinson's Disease (PD) can be significantly improved by using the Quantitative Susceptibility Mapping (QSM) based iron mapping techniques with the goal of validating QSM for potential use in later clinical trials. This study will include six cohorts - Parkinson's Disease (PD) Stage I (20 subjects), PD Stage II (20 subjects), PD Stage III (20 subjects), PD Stage IV (20 subjects), REM Sleep Behavior Disorder (RBD) (10 subjects), and healthy controls (10 subjects). Subjects who meet the inclusion and exclusion criteria and whom sign an informed consent form will be eligible for participation in this study and will undergo the following assessments regardless of cohort stratification. Screening and Baseline: Subjects will be seen in the Movement Disorder Clinic within the Department of Neurology at Weill Cornell Medicine, or at HSS, or at Cornell Ithaca (other recruiting sites) for an in-office visit which will include review of medical history, concomitant medication review, physical exam, urine pregnancy test (females of childbearing potential age) and completion of clinical surveys. This visit may be a standard of care, office visit, or may be an office visit performed for research purposes. If standard of care, in-office neurological assessments have already been performed within three months of study imaging, this may be used to satisfy the study baseline/screening and 24 month in office assessments. All subjects, whether recruited at WCM or HSS, will receive either a PE2i Positron Emission Tomography (PET) scan or DaT single photon emission computed tomogrpahy (SPECT) scan, and Magnetic Resonance Imaging (MRI) scan of the brain at WCM. If the subject received a standard of care MRI scan of the brain within 1 month of screening, this exam will be utilized to satisfy the baseline requirement for an MRI of the brain. However, if a standard of care MRI of the brain was performed either at an outside facility or at New York Presbyterian-Weill Cornell Medicine outside the required 1 month window to enrollment, the MRI of the brain will be repeated at Baseline as performed for research purposes. Month 24 (+/- 2 Months): Subjects will be seen in the Movement Disorder Clinic within the Department of Neurology at Weill Cornell Medicine, or at HSS for an in-office visit (either as a standard of care office visit, or may be an office visit for research purposes) which will include review of medical history, review concomitant medications, physical exam, urine pregnancy test (females of childbearing potential age), complete surveys; and subjects will receive a repeat PE2i PET scan or DaT scan and MRI of the brain at WCM. The following outlines which procedures are considered performed for research purposes vs. performed for standard of care purposes for PD and RBD Cohorts: Performed for Research Purposes: PE2i PET Scan or DaT scan performed at Baseline and Month 24 visit; MRI of the brain performed at Baseline (only if repeated for research purposes as outlined above) and Month 24 visit; Urine pregnancy test for female subjects of child-bearing potential age performed at baseline and Month 24 visit. Performed for Standard of Care Purposes: Office visit performed at Baseline and Month 24 visit (unless subjects are asked to return for an office visit performed for research purposes with the Neurology team at WCM or HSS); MRI of the brain performed at Baseline visit; Completion of clinical neurological surveys (e.g. UPDRS). Subjects recruited at Cornell Ithaca will have the MRI at the Cornell MRI Facility and may or may not have a PE2i PET scan or DaT scan at WCM. Subjects who receive the DaT scan will have to take Lugol's solution before scanning to protect their thyroid.

Our primary objective is to establish that Quantitative Susceptibility Mapping (QSM) is more sensitive than R2* for nigral iron mapping in monitoring PD iron overload.

Our secondary objective is to evaluate rate of iron accumulation throughout different disease stages. 1. Unified Parkinson's Disease Rating Scale (UPDRS) scores to monitor for clinical changes. 2. Quantitative PE2i PET scan estimations to monitor for dopaminergic degeneration.

INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria:

1. Idiopathic Parkinson's Disease, REM sleep behavior disorder subjects without signs of Parkinsonism and normal healthy controls.
    a. If tremor is not present, subjects must have unilateral onset and persistent asymmetry of the symptoms.
    b. For PD subjects only: age > 30 years at time of diagnosis of PD with a maximum age of 100 years old.
    c. Hoehn & Yahr stage < V (if PD)
2. For PD subjects only: receiving an optimized dopaminergic regimen (i.e., either MAO-B inhibitor, a dopamine agonist and/or low doses of L-dopa, with dose change no more frequent than every 6-months in the course of the study); or medications naïve
3. No overt anemia, iron deficiency, or other hematological disorders
4. Deemed healthy and able to undergo MRI and PE2i PET imaging by the site investigator, based on screening assessments—medical history, physical examination
5. For controls and REM sleep behavior disorder subjects only: age 20-80; willing to undergo multiple imaging sessions
6. Signed informed consent form

Exclusion Criteria:

1. Patient with atypical parkinsonism (such as suspected Progressive Supranuclear Palsy, Multiple System Atrophy) and secondary parkinsonism (such as normal pressure hydrocephalus, drug-induced, or vascular parkinsonism)
2. Patients with uncertainty as to having classical Parkinson's disease, such as those who might have scans without evidence of dopaminergic deficits (SWEDDs)
3. Presence of a medical or psychiatric comorbidity that can compromise participation in the study
4. Patients with clinically significant depression as determined by the Beck depression score > 15
5. History of exposure to typical or atypical neuroleptics or any dopamine blocking agent within 6 months prior to enrollment
6. Patients with psychosis/active hallucinations and memory difficulty pre-dating the onset of motor symptoms

7. History of brain surgery for PD
8. Untreated thyroid disease
9. History of stroke or cerebral vascular disease
10. History of drug abuse
11. History of repeated head injury or encephalitis
12. Positive dementia by DSM IV-R
13. Women of childbearing potential who are not surgically sterilized have to use a reliable measure of contraception and have a negative urine pregnancy test at the screening
14. Participation in other investigational drug trials within 30 days prior to screening
15. Contraindication for receiving MRI imaging such as presence of pacemakers, certain types of metallic implants, severe claustrophobia, history of reaction to contrast material, or renal insufficiency.

DATA AND SAFETY MONITORING PLAN

To assess both safety and efficacy of PE2i study procedures, intra-imaging monitoring will be performed to assess subject safety. In addition, subjects will return for in-office physician visits at designated time points (baseline and 24 months) where physical exam, vital check, and adverse events will be assessed and tabulated.

There are no defined stopping rules however, in the event that the FDA, IRB, or other regulatory agencies request stoppage, all study activities would be immediately halted. The goal of the study is to to establish an accurate and sensitive QSM-based SNc iron mapping method through observation only so there is no therapeutic intent and, thus no defined stopping rules. Circumstances for subject termination/dropout due to study-related adverse events are highlighted in the adverse events-related termination section listed below.

Adverse events that may cause termination/dropout of a subject: generally, inability to tolerate the study procedures, imaging: claustrophobia during imaging studies or inability to obtain venous access.

Anticipated adverse events and risks of study interventions:

1. Pe2i scans. Subjects may experience discomfort from lying still on their back for each scan; Some people feel claustrophobic in the PET scanner. If this happens the scan will stop immediately. PE2i-PET scans are experimental studies that may be conducted only for medical research purposes. PE2i-PET involves exposure to radiation, and that exposure is increased the more often such tests are done. Radiation exposure at certain doses can potentially cause cancer. The PE2i tracers are radioactive because one of the atoms (Carbon-11) that make up the drug has been man-made in such a way that it will spontaneously decompose. When it does, it will give off a type of radiation in the form of rays. These special type of rays are a form of radiation that cannot be seen with the human eye, but the PET camera has sensors that can detect where it is coming from inside your body. These rays will be used to make pictures of the subject's brain. The total amount

of radiation that subjects will be exposed to from the PET scans in this study is a little less than the amount of radiation exposure allowed for occupational workers over a period of one year. There are always theoretical risks associated with exposure to radiation of any kind, including the risks of developing cancer and hardening of the arteries. These risks are considered within acceptable limits for human subjects who will not personally benefit from their participation in the research study.

2. Allergic reactions. With any drug (radioactive chemical substance used in PE2i PET scans), there is a possibility of an allergic reaction. Allergic reactions most commonly are mild such as a rash, cough, dizziness, or fainting, hives, itching, chest tightness, shortness of breath or wheezing. Rarely, a more severe and possibly even life-threatening reaction can occur, such as anaphylaxis (a reaction which may involve shortness of breath, swelling or closing of the airway and/or drop in blood pressure). In the event of an allergic reaction, medical treatment will be immediately available from the study staff. The risks of an allergic reaction from imaging exams in this study are very low.

3. IV catheter. Before each PE2i PET scan study begins, a catheter will be placed in the subject's forearm. Catheter placement may cause bleeding, bruising, redness, swelling discomfort, and/or pain at the needle site or dizziness and fainting. The bruising and discoloration at the areas where the venous catheters are inserted may last for several days after the study. On rare occasions, they may cause clot formation and infection. The subject will be instructed to notify the study physician right away if symptoms are caused from the IV catheter.

4. MRI scans. There are no known risks or adverse effects resulting directly from exposure to magnetic fields and radiofrequency signals used in the MRI imaging other than the potential risks associated with the scanning procedure summarized below: A. Claustrophobia. Some subjects may feel claustrophobic in the MR scanner. If this happens the study team will stop the scan immediately. B. Metallic Foreign Body Risks. Subjects may not be able to undergo MRI scanning if they have pacemaker, or certain other implanted electronic or metallic devices. Subjects will be screened for MRI contraindications during the screening visit.

5. DaT scans. The most common side effects of DaT imaging are headache, increased appetite, and dizziness. However, it is important for you to know that the injection of DaTscan may include risks that cannot be predicted, although for the purposes of this study, it is being used in accordance with its FDA approved usage. The insertion of the IV may feel uncomfortable and may leave a bruise. You will need to lie very still under the camera for up to 1 hour, which may be uncomfortable. The DaT scan included in this study is employed routinely in the care of patients with medical conditions. It involves exposure to radiation and that exposure is increased the more often such tests are done. Radiation exposure at certain doses can potentially cause cancer. Any possible increase in cancer risk associated with participation in this study is within acceptable limits for human research subjects.

In order to immediately recognize the adverse events that do occur, appropriate screening will be performed, including -physical exam, vitals signs, urine pregnancy test to verify eligibility before initiating any study related procedures. On the day of PE2i PET or DaT scan imaging, subject's vital signs will be taken and injection-site tolerance will be assessed after the injection of radioactive material. Any assessment of adverse events will be documented and reported as necessary.

To minimize any negative impact on subjects resulting from study closure or a subject being terminated from the study: in the event of premature discontinuation, subjects will receive adequate clinical follow-up from their treating physicians in accordance with standard of care follow up guidelines.

Appropriate screening will be performed, including physical exam, vital signs, urine pregnancy test to verify eligibility before initiating any study related procedures. On the day of PE2i PET or DaT scan imaging, subject's vital signs will be taken and injection-site tolerance will be assessed after the injection of radioactive material. Any assessment of adverse events will be documented and reported as necessary.

In the event of premature discontinuation, subjects will receive adequate clinical follow-up from their treating physicians in accordance with standard of card follow up guidelines.

Adverse events will be graded on severity, attribution, and expectedness. All AEs whether related or not, anticipated or not, will be reported to the IRB. Severity defined as: Mild: the subjects is aware of the sign or symptom, but it does not interfere with his/her usual daily activities and/or it is of no clinical consequence. Moderate: the AE interferes with the usual daily activities of the subject of it is of some clinical consequence. Severe: the subject is unable to work normally or to carry out his/her usual daily activities, and/or AE is of definite clinical consequence. AE's will be reported to the WCMC IRB as they occur. According to local requirements, the study team will communicate relevant safety information to the appropriate agency(ies), IRB, and/or all active investigators as it becomes available.

We will be using a medical monitor. The monitor will be affiliated with WCMC-NYP and is a part of the research study.

STATISTICAL ANALYSIS PLAN

Clinical outcome assessments: The six subject cohorts will be compared to assess differences in their clinical evaluations and MRI iron measurements obtained in this study. MRI iron measurements will be correlated with clinical evaluations to estimate iron overload effects at baseline visit and month 24 visit after enrollment. Also, these MRI iron measurements will be correlated with rate of dopaminergic loss if detected by PE2i PET or DaT scan imaging. Statistical analyses: All analyses will be performed using a statistical software (SPSS, Chicago, IL). The kappa test will be used to assess reader agreements, and covariance analysis (adjusted for baseline differences) to estimate clinical outcomes as measured by UPDRS at baseline and 24 Months, and PE2i PET or DaT scans at baseline and 24 Months. For non-normally distributed data, the robustness will be checked after log transformation. The analysis of variance assumption will be validated by residual analysis, and the size effect will be adjusted for baseline differences. Correlation and logistic regression will be performed among various MRI and PE2i PET or DaT scan measurements and other clinical data. The longitudinal data will be modeled using the generalized estimating equation (GEE) to assess significant change. Paired t-test and ROC curve comparison will be performed to assess differences between QSM and R2*.