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SUMMER 2019

Featured Study: TANGLES

Human CNS Tau Kinetics in Tauopathies

The TANGLES study was established to provide a better understanding of the role that the protein tau has in neurodegenerative disorders. Tau is a protein that can form tangles in neurons in the brain and leads to neurodegenerative disorders in individuals called tauopathies. Understanding of the metabolism processes of tau — how it is made, transported, and cleared in the human body — is important in designing future treatments and diagnostic tools to target this protein.

Persons diagnosed with Progressive Supranuclear Palsy (PSP), Corticobasal Degeneration (CBD), or Frontotemporal Dementia due to MAPT mutations are eligible. Biological family members of MAPT mutation carriers also can participate. This study is still recruiting. If you are interested in participating, you can learn more below and contact the study coordinators listed at the end of this article.

CHALLENGES FINDING QUALIFIED PERSONS FOR THIS STUDY

This is a two-year clinical trial that has been set up to observe 32 participants. Only 20 of the slots have been filled because it has been challenging to find eligible people, said Dr. Nupur Ghoshal, an Associate Professor of Neurology and Psychiatry at Washington University School of Medicine in St. Louis, Missouri, and one of the study's principal investigators (PI). The other PI is Dr. Randall Bateman, the Charles F. and Joanne Knight Distinguished Professor of Neurology at the university. Dr. Bateman led the development of a technique known as stable isotope-linked kinetics or SILK that helps determine whether the clearance of amyloid beta is impaired in patients.

"Sometimes it is really tough to determine whether a person is a fit for the study," explained Dr. Ghoshal. "A CBD diagnosis doesn't have to be a tauopathy, so we have to delve deeper and see if the person really fits."

Finding people with PSP to qualify is most challenging, she said as people diagnosed with CBD or PSP are pretty rare. "We have to be careful with diagnosing people with PSP. We have to be sure, and that takes time. But over time these people become less mobile, which creates challenges for them to participate" in the trial.

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The TANGLES study, which is privately funded, reimburses participants and a care partner up to $1,200 for time, effort, and travel expenses. This has enabled people from as far away as New York and Canada to travel to St. Louis, she said. In addition, after working out Institutional Review Board (IRB) and United Kingdom regulations, a specialty site in London, England, has reached five qualified people who have all joined the clinical trial.

Each participant, accompanied by a care partner, makes six visits to the study site over a four-month period. The study team can assist participants with travel arrangements or transport needs such as wheelchairs.

The initial visit requires an overnight stay and involves an intravenous infusion, lumbar puncture, and blood draw. During each of the five subsequent visits, participants undergo a lumbar puncture and blood draw.

"The first clinical trial visit is the longest, and from the participant side the scariest," Dr. Ghoshal noted, particularly due to the unknown of the lumbar puncture, or spinal tap. "They (lumbar punctures) get a lot of bad press. I talk with them as I'm working. Often they don't realize that the needle is in and out and I'm done, and they're wondering when I'm going to start."

STUDY OUTCOMES

Clinical trials and other research studies take time. Slowly the data is gathered, and gradually the results provide insights.

TANGLES

Human CNS Tau Kinetics in Tauopathies

"We are measuring more precisely. Tau PET imaging capabilities are growing," noted Dr. Ghoshal. "We think we are seeing groupings among these tauopathies. Are they always clustered together? But then we see a one-off finding with one person that is different."

Then there is determining whether too much tau is being made or is enough tau being made but not clearing out? If there is too much tau, "we need to knock it down and get rid of the excess," she said.

Some in her professional circle feel hopeful that interventions are three to five years out. Recently, Dr. Bruce Miller, Professor in Neurology at the University of California, San Francisco, said during the May 5, 2019, 60 Minutes report on frontotemporal dementia that he is hopeful in five years there will be powerful therapies, particularly for behavioral variant and language variant FTD. Dr. Miller also directs the UCSF Memory and Aging Center and the Global Brain Health Institute.

"The arsenal is there; tools are being developed," Dr. Ghoshal said enthusiastically. "It is an interesting time in the field."

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READ MORE ABOUT DR. NUPUR GHOSHAL

LEARN MORE ABOUT TANGLES ON CLINICALTRIALS.GOV

TANGLES STUDY

Title: Human CNS Tau Kinetics in Tauopathies (TANGLES)
ClinicalTrials.gov identifier (NCT number): NCT03545126
Sponsor: Washington University School of Medicine in St. Louis, MO
Collaborators:

- Association of Frontotemporal Degeneration (AFTD)
- Tau Consortium

Funding: Private

Summary:
The goal of this study is to characterize tau kinetics and tau aggregation in the human CNS and to test the hypothesis that tau kinetics are altered (i.e. increased production, decreased clearance, and increased aggregation rate) in tauopathies.

Who is Eligible:

- Progressive Supranuclear Palsy (PSP) = 12
- Corticobasal Degeneration (CBD) = 8
- Frontotemporal Dementia (FTD MAPT Mutation) = 12

Intervention/Treatment: 13C6 Leucine

Detailed Description:
Tauopathies are neurodegenerative diseases with tau pathology. These tauopathies are the most common pathology in neurodegenerative diseases, and they are reaching epidemic proportions. The rates of tau kinetics are central to understanding normal and abnormal processing and production and clearance of tau kinetics in humans to help understand the causes of tauopathy and evaluate tau-targeted therapeutics.

This study will utilize the Stable Isotope Labeling Kinetics (SILK) method to elucidate tau kinetics in vivo in the human central nervous system (CNS) and its alteration in tauopathies. A total of ~32 participants from 3 different neurodegenerative diseases: Frontotemporal Dementia (FTD), Corticobasal Degeneration (CBD), and Progressive Supranuclear Palsy (PSP), will be invited to enroll in the study.

Participants will be labeled with stable isotopes via 16hr intravenous infusion and CSF samples collected during subsequent lumbar puncture visits over ~120 days. CSF will be analyzed over time for the quantitation of labeled tau.

Study Type: Observational
Observational Model: Case-Control
Time Perspective: Prospective
Start Date: August 21, 2017
End Date: December 31, 2019
Estimated Enrollment: 32 participants
Age Requirements: Age 18 and older
Inclusion Criteria: Diagnosed with PSP, CBD, or FTD MAPT

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Group Requirements:

- PSP — Recruited participants will be given 13C6 Leucine through intravenous infusion (4 mg/kg/hr for 16 hours), and CSF will be collected five times over 120 days (on approximately days 1-4, 5-10, 11-20, 21-60 and 61-120) after labeling.
- CBD — Recruited participants will be given 13C6 Leucine through intravenous infusion (4 mg/kg/hr for 16 hours), and CSF will be collected five times over 120 days (on approximately days 1-4, 5-10, 11-20, 21-60 and 61-120) after labeling.
- FTD MAPT — Family members with or at-risk of tau mutations (e.g. P301L). Recruited participants will be given 13C6 Leucine through intravenous infusion (4 mg/kg/hr for 16 hours), and CSF will be collected five times over 120 days (on approximately days 1-4, 5-10, 11-20, 21-60 and 61-120) after labeling.

Exclusion Criteria:

- Clotting disorder
- Active anticoagulation therapy
- Active infection
- Meningitis
- Recent syncope
- Current experimental treatment targeting Aβ or medications thought to influence Aβ production or clearance rates (benzodiazepines, muscarinic agents, or anti-epileptics)

Outcome Measures:

- Primary — Tau Fractional Turnover Rate (FTR) [Time Frame: 6 months]
  Calculated by using CSF tau labeling and plasma free leucine.
- Secondary — (1) CSF Tau Absolute Concentration [Time Frame: 6 months]
  Measured using labeled and unlabeled tau protein isoforms that will be immunoprecipitated and analyzed by mass spectrometry.
  (2) Tau Production Rate [Time Frame: 6 months]
  Measured by FTR multiplied by CSF tau concentration.

Study Site Information:

- Primary — Washington University in St. Louis School of Medicine
- Secondary — London, England, UK

Investigators:

- Principal Investigator: Randall Bateman, M.D., Washington University in St. Louis Medical School
- Principal Investigator: Nupur Ghoshal, M.D., Ph.D., Washington University in St. Louis Medical School

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