Children's Hospital of Philadelphia

Annual Progress Report: 2010 Formula Grant

Reporting Period

January 1, 2011 – June 30, 2011

Formula Grant Overview

The Children's Hospital of Philadelphia received $3,548,977 in formula funds for the grant award period January 1, 2011 through December 31, 2014. Accomplishments for the reporting period are described below.

Research Project 1: Project Title and Purpose

Magnetic Resonance Imaging and Neurocognitive Assessment in Chronic Kidney Disease - Utilizing state of the art neuroimaging technology, including standard MRI, arterial spin labeling, resting state functional MRI, and a concurrent matched control group in a cross-sectional study of 180 individuals, aged 8-25 years, we will test the mechanistic hypothesis that subclinical vascular disease affects cognitive function in chronic kidney disease (CKD). Using novel pattern recognition methods, we will integrate these measurements to develop a multi-parametric imaging phenotype in CKD that can identify high risk groups. We hypothesize that level of kidney function, hypertension and anemia affect resting cerebral blood flow and functional performance. Achievement of our aims will enable targeted interventions to prevent and treat the cognitive deficits associated with CKD, and improve the quality of life for this vulnerable population.

Anticipated Duration of Project

1/1/2011 - 12/31/2014

Project Overview

To identify the causal mechanisms underlying the cognitive decline seen in Chronic Kidney Disease (CKD), we propose to use state of the art multimodal magnetic resonance imaging (MRI) and cognitive testing in a cross-sectional study of 90 subjects with Stage III, IV and V CKD (estimated GFR <60 ml/min/1.73m2), aged 8 – 25 years and 90 controls matched on age and maternal education. Our specific aims are:

1. To demonstrate differences in brain imaging between the group of individuals with CKD and age-matched controls, manifested by a higher prevalence of subcortical hyperintensities on T2-weighted (FLAIR) MRI and reduction in arterial spin labeling (ASL) signal in subjects with CKD. We hypothesize that hypertension (HTN) and anemia in CKD cause alterations in cerebral blood flow (CBF) which will be quantified using ASL perfusion MRI, as well as

hypoxic-ischemic injury in the brain, which can be measured via multi-parametric MRI (combination of FLAIR, T2, PD and T1-weighted images).

2. To explore the impact of CKD on structural brain integrity as measured by anatomic MRI with quantitative volumetric measurements with a particular focus on prefrontal cortex and frontotemporal regions. We hypothesize that evidence of frontotemporal brain injury will be correlated with deficits in executive function in subjects with kidney disease.

3. To characterize the impact of longer duration and increased severity of CKD, HTN and anemia on neurocognitive abilities and correlate these with fMRI findings. We hypothesize that cognitive deficits will be correlated with changes in regional CBF and/or connectivity within specific brain networks supporting these neurocognitive functions.

4.To develop individual-patient biomarkers by combining structural, ASL and fMRI data in multi-parametric classification. Our goal is to ultimately find imaging patterns that in future studies can predict high risk of neurocognitive decline and thereby identify subjects for targeted interventions.

This will be the first study to use multimodal MRI to study the neurological consequences of CKD in a pediatric population. A multidisciplinary team of senior investigators with a strong track record of success in translational neuroimaging research will oversee this project.

Principal Investigator

Susan L. Furth, MD, PhD
Professor, Pediatrics
Children's Hospital of Philadelphia
3615 Civic Center Boulevard
Philadelphia, PA 19104

Other Participating Researchers

Divya Moodalbail, MD; Kevin Meyers, MD Jerilynn Radcliffe, PhD; Robert Schultz, PhD – employed by Children's Hospital of Philadelphia
Christos Davatzikos, PhD; John Detre, PhD - employed by University of Pennsylvania
Employed by University of North Carolina: Stephen Hooper, PhD - Consultant

Expected Research Outcomes and Benefits

We will identify differences in brain structure and functional performance between CKD and control group children and young adults. Structural MRI (sMRI) will assess the regional distribution of grey matter, white matter and cerebrospinal fluid (CSF), which will determine whether there are correlations between CKD related clinical variables, brain atrophy and cognitive performance, and whether or not these relationships are spatially heterogeneous. sMRI will provide measurements of the regional distribution of cerebrovascular disease (CVD), as HTN is exceedingly common in CKD and is one of the highest risk factors for CVD.

Additionally, ASL MRI will provide measurements of regional blood perfusion, which will provide mechanistic insights into the pathogenesis of observed structural changes based on correlations between CKD-related clinical variables, brain atrophy and cognitive performance, and whether or not these relationships are spatially heterogeneous. Using both ASL MRI and resting state fMRI we will examine brain activity in the absence of external stimuli and this will allow us to evaluate functional changes in these patients that correlate with clinical and cognitive variables. State of the art pattern recognition methods will allow us to integrate all these types of measurements and develop a multi-parametric imaging phenotype in CKD.

This phenotype can be used to predict subsequent cognitive decline in future longitudinal studies so that interventions can be implemented to improve functional performance in this population. We are studying children and young adults with CKD, as this will allow us to identify neurocognitive and neuroanatomic changes due to kidney disease in the absence of underlying CVD, which is ubiquitous in adults with CKD. The long term benefit of this project will be improvement in the health status of the 1 in 9 Americans with CKD, as cognitive impairment may affect adherence to the complex medical regimens which these patients are routinely prescribed, and may contribute substantially to decreasing the adverse outcomes and substantial cost associated with End Stage Renal Disease (>$36 billion in 2007).

Summary of Research Completed

During this reporting period, 6 of 6 milestones were met:

1. Steering Committee
The steering committee for this study has been established, including Drs. Susan Furth, Christos Davatzikos, John Detre, Stephen Hooper, Jerilynn Radcliffe, and Robert Schultz. The committee met on January 19, 2011 and March 25, 2011, and will continue to meet in person on a scheduled quarterly basis. In addition, the committee will meet by conference call twice per month beginning in June 2011 to discuss study progress.

2. Hire dedicated study coordinator
The position was posted on the Children's Hospital of Philadelphia's (CHOP) career website. Many applications were received and several candidates were interviewed. Katie Reiser joined the study team on February 7, 2011, as a full time research coordinator. Her training has included working closely with Dr. Robert Schultz's team members at the Center for Autism Research, who have extensive experience with neuroimaging and neurocognitive protocols at CHOP. Additionally, she has undergone human subjects protection training, radiology safety training, and training in REDCap database development and management.

3. Screen nephrology clinic appointment list for eligible subjects
The study coordinator has created a tracking database to monitor all new and continuing patients in the outpatient nephrology, transplant, and dialysis clinics at CHOP. Each week, patient data including diagnosis, race, gender, age, and estimated eGFR are entered to the log as part of IRB-approved pre-screening procedures.

To date, 200 patients have been screened and 29 of these are potentially eligible to participate in the study. 15 of the eligible patients are transplant recipients. Reasons for ineligibility are given below in Table 1. Of the 29 potential subjects, 16 are male and 13 are female. These numbers, shown in Table 2, are in line with the population seen in the clinic (Total Screened). The racial breakdown for potential subjects is 16 Black, 9 White, 3 Other, and 1 Asian. 4 are of Hispanic ethnicity. The percentage of Black and Hispanic eligible patients is higher than the overall clinic population (Tables 3 and 4). The most common underlying diseases for potential subjects are summarized below in Table 5. Diagnoses common to more than one eligible patient are shown. Many patients have more than one diagnosis.

Table 1

Reason Ineligible	**eGFR >60**	**Unavailable eGFR**	**Age <8 or >25**	**Total Ineligible**
Number	89 (52%)	25 (15%)	57 (33%)	171

Table 2

Gender	**Male**	**Female**
Total Screened	114 (57%)	86 (43%)
Total Eligible	16 (55%)	13 (45%)

Table 3

Race	**Black**	**White**	**Asian**	**Other or Missing**
Total Screened	76 (38%)	85 (43%)	9 (5%)	30 (15%)
Total Eligible	16 (55%)	9 (31%)	1 (3%)	3 (10%)

Table 4

Ethnicity	**Hispanic**	**Non-Hispanic**
Total Screened	19 (10%)	181 (90%)
Total Eligible	4 (14%)	25 (86%)

Table 5

Diagnosis	**Number of patients eligible for study**
CKD	12
FSGS	6
Obstructive Uropathy or posterior urethral valve (PUV)	4
Nephrotic Syndrome	2
Dysplasia	2
Glomerular nephritis	2

4. Fill post-doctoral positions

The position was posted on the CHOP career website and many applications were received. A candidate has been interviewed, references obtained and an offer made for a planned start date of July 1, 2011.

5. Develop data collection forms and database for data entry

Informed consent forms and seven case report forms have been created for this study to collect contact information and data on study eligibility criteria, MRI eligibility, medical history, family history, developmental history, blood lab results, urine lab results, physical examination results,

and medication regimen. An IRB-approved REDCap database has been constructed to accommodate this study and has undergone extensive development including variable coding, branching logic, and mock data export and analysis. These steps ensured that the database is operational, efficient, and user-friendly. Data will be entered directly to the electronic database.

6. Implement protocol
The study has been introduced to the entire clinical team in the Nephrology division at CHOP. Each clinician is aware of the study and regularly recommends eligible patients to the research team.

At the request of the Children's Hospital of Philadelphia's Institutional Review Board, minor amendments to the protocol have undergone review and were approved on April 27, 2011. These included detailed radiology sequence procedures, the addition of a computerized neurocognitive battery, and a detailed plan for recruiting healthy volunteers.

The study team met with members of the Radiology Division at CHOP to prepare for enrollment, including the Vice Chair of Research, scheduling manager, information services manager, and all technologists. An optimization procedure (imaging on a mock test subject) was performed and the results analyzed to confirm the parameters chosen will yield the desired results. This procedure identified artifact in structural functional magnetic resonance imaging (fMRI) and inadequate parameters in proton density and T_2 images that have since been resolved in the sequence protocol. A data-sharing network was created using Dr. Robert Schultz's server at the Center for Autism Research and SFTP server accounts at the University of Pennsylvania for access by Drs. Davatzikos and Detre.

The study coordinator met with the nursing and neurobehavioral staff at the Clinical and Translational Research Center (CTRC) at CHOP to prepare for enrollment.