Title of Project:

Evaluation of Intravoxel Incoherent Motion in the Spinal Cord of Multiple Sclerosis Patients

Abstract:

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) which leads to demyelination and neurodegeneration[1]. MS affects mobility, balance, vision, and cognition making it the leading cause of non-traumatic disability in young adults worldwide[2]. In spite of its global prevalence little is known of the etiology of MS and its progression is highly variable. Advanced magnetic resonance imaging studied have helped better understand the pathophysiology of the disease and have revealed alterations in perfusion. However, all perfusion magnetic resonance studies to date have focused on the brain and have not focused on the spinal cord. Understanding the pathogenesis of MS in the spinal cord is crucial in the diagnosis and prognosis of the disease. In this study we propose to utilize incoherent intravoxel motion (IVIM), a non-contrast perfusion technique, assess perfusion in the spinal cord of patients diagnosed with MS.

Itemized Budget:

**please use this section as a reference when completing the budget portion of your application.*

MRI Scans:

Scanning @ $1200/hr., minimum 15 min increment = $300/subject
-Total = 40 subjects x $300/scan = $12,000

Subject payment:

$10/subject for participation
-Total = 40 subjects x $10 = $400

Travel:

Travel for U.S. researcher to present at U.S. and U.K meetings = $4500
Travel for U.K. researcher to present at U.S. and U.K meetings = $4400

-Total = $8900

Travel estimates provided by ASRT

	U.S. Researcher	**U.K. Researcher**
Travel to U.S. meeting	$700	$1800
U.S. hotel	$900	$900
U.S. meals (3 days)	$180 (2019 Fed per diem rate)	$180
Travel to U.K. meeting	$1800	$600
U.K. hotel	$700	$700
U.K. meals (3 days)	$180	$180
Total	$4460 (**$4500**)	$4360 (**$4400**)

Equipment:

4 TB solid state hard drive for data backup and storage = $400

(Only 1 hard drive is needed to pull imaging data from the scans performed on the MRI scanner and serve as a hardcopy of the data. Once data is off the scanner it can be shared and stored via cloud-based platforms for easy access to both U.S. and U.K researchers from anywhere.)

1 High performance computer for data processing = $2400

(Only 1 computer is needed to perform the appropriate data post-processing steps and needs to meet minimum computing power requirements to be able to perform all post-processing steps. Remote desktop access can be setup to again allow for easy access to both U.S. and U.K researchers from anywhere.

-Total = $2800

PI Wages:

U.S. researcher: 4.2% effort = $2730

U.K. researcher: 3.8% effort = $1976

(U.K. research effort reflects the same amount of effort as the U.S. researcher minus the scanning time to acquire the data, as that will be performed by the U.S. researcher. Moreover, salary for U.K researcher is estimated based on 90th percentile of salary for U.K. MRI Radiographer from https://www.payscale.com/research/UK/Job=Radiographer/Salary).

-Total = $4706

PI Benefits:

U.S. researcher: 25% of wage = $682.5

U.K. researcher: 25% of wage = $494

-Total = $1176.5

-Grant Total = $29,982.5

Statement of Problem: Background and Significance:

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) which leads to demyelination and neurodegeneration[1]. MS affects mobility, balance, vision, and cognition making it the leading cause of non-traumatic disability in young adults worldwide[2]. In spite of its global prevalence little is known of the etiology of MS and its progression is highly variable. Early and accurate diagnosis of MS is critical and is done through a combination of reported clinical symptoms and positive radiological findings on magnetic resonance imaging (MRI)[3]. However, a majority of MRI studies on MS focus on the brain overlooking the spinal cord[4]. This paucity of MS spinal cord research is despite 90% of MS patients showing spinal cord abnormalities on conventional MRI[5]. Imaging of the spinal cord plays an important role in the diagnosis of MS and provides prognostic information[3]. MS associated pathological changes in the spinal cord are complex and include demyelination, inflam gliosis and axonal loss[6]. Although conventional T2 weighted or proton density weight MRI sequences can detect focal MS lesions they lack sensitivity and specificity for evaluating diffuse pathological changes in the spinal cord do to MS[4]. In order to come up with effective MS treatments a deeper understanding of the spinal cord pathogenesis is needed and is possible with new development of more advanced MRI techniques[7]. Advanced MRI techniques, like perfusion-weighted imaging (PWI), allow for in-vivo assessment of perfusion[8]. PWI shows promise for being a sensitive tool to image changes in MS pathophysiology and improve early detection compared to conventional MRI[8]. These advanced methods allow for quantitative MRI and can provide potential biomarkers for the evaluation of MS treatments[9]. Prior research using PWI has identified alterations in cerebral perfusion in subjects with MS[10-12]. Moreover, pathological findings support the idea of vascular involvement[9] and have documented impaired cerebrovascular reactivity in patients with MS[13-15]. PWI MRI techniques can be categorized into contrast and non-contrast techniques. Contrast based PWI techniques require the administration of gadolinium-based contrast agents (GBCA). However, the use of GBCA has come under scrutiny recently with reports confirming deposition of gadolinium in the brain[16]. This is of special concern in the MS population as they undergo serial imaging with GBCA[17]. Therefore, a non-contrast PWI technique called, intravoxel incoherent motion (IVIM), will be used in this study in hopes of improving patient safety. IVIM allows for characterization of perfusion during diffusion-weighted imaging (DWI) as the signal attenuation at low b-values is the composite of both diffusion and perfusion[18]. Previous research has shown IVIM to be effective in multiple body parts for differentiating benign and malignant lesions[18] and has shown good correlation with perfusion metrics from physiologically and pharmaceutically induced changes[19,20]. IVIM besides being a non-contrast method also provides several other key benefits as the technique of choice to assess spinal cord perfusion in MS patients. IVIM requires a slight modification to the DWI sequence, which allows for simultaneous by allowing simultaneous measurement of the apparent diffusion coefficient (ADC), a clinically accepted metric in differentiating MS lesions[21] and registration of perfusion and diffusion data. This small change to the DWI sequence to allow for IVIM acquisition means that there is a very small increase to the overall scan time for MS patients eliminating the need to run an addition dedicated PWI scan to assess perfusion. Moreover,

IVIM relies more on post-processing than acquisition making the technique more widely transferable and easier to implement on most MRI scanners as compared to other non-contrast PWI techniques like arterial spin labeling. PWI appears to be a more sensitive tool compared to conventional MRI for evaluating changes in MS disease progression and assessment of perfusion alterations in the spinal cord is highly warranted.

Specific Aims: Objectives, research and significance:

MS is one of the leading causes of disability in young adults worldwide yet current understanding of spinal cord pathology in MS remains incomplete. MS associated pathological changes in the spinal cord are complex and include demyelination, inflammation, gliosis and axonal loss. One area that shows promise in elucidating the progression of MS is in the assessment of perfusion. Compromised perfusion in MS has been identified in histopathological and imaging studies. Advancements in MRI techniques could further elucidate insights into the pathophysiology of MS and serve as a valuable tool for diagnosis and patient follow-up. Moreover, quantitative PWI MRI methods including incoherent intravoxel motion (IVIM) could help establish biomarkers to help improve diagnosis, monitor disease progression, and improve the quality of clinical trials. The central hypothesis is that axonal damage from the progression of MS from demyelination creates a lower parenchymal metabolic demand resulting in hypoperfusion of the spinal cord.

The aim of this research is threefold:
Specific Aim 1: To provide the first reports of perfusion-weighted imaging (PWI) MRI in the spinal cord of patients with multiple sclerosis.

Specific Aim 2: Assess the utility of intravoxel incoherent motion (IVIM) as a non-contrast PWI technique compared to provide perfusion metrics compared directly to commonly accepted diffusion weighted imaging (DWI) metrics.

Specific Aim 3: Provide preliminary evidence for a clinically feasible and implementable MS scanning protocol that allows for the assessment of perfusion in MS without the administration of gadolinium with only a minimal time penalty for the patient.

Literature Review:

Multiple sclerosis (MS) is a chronic inflammatory disease of the central nervous system (CNS) which leads to demyelination and neurodegeneration[1]. MS affects mobility, balance, vision, and cognition making it the leading cause of non-traumatic disability in young adults worldwide[2]. In spite of its global prevalence little is known of the etiology of MS and its progression is highly variable. Early and accurate diagnosis of MS is critical and is done through a combination of reported clinical symptoms and positive radiological findings on magnetic resonance imaging (MRI)[3]. MS is categorized as either relapsing-remitting or primary progressive, with the majority of patients being diagnosed with relapsing-remitting MS.

Relapsing-remitting MS most commonly affects young people with the average presentation of symptoms occurring at 30 years old with a predominance of cases being diagnosed in women[3]. Relapsing-remitting MS consists of time periods of neurological dysfunction or relapse, followed by periods of remission with no symptoms[22]. Primary progressive MS patients on the other hand show a slow and progressive decline in neurological function over time[23]. However, patients with relapsing-remitting MS can progress into secondary primary progressive MS when the disease course switches and there are no relapses, just a steady increase in disability [23].

The pathogenesis of MS is not completely understood, however, there is growing evidence that a vascular component may contribute to the progression of the disease [24-26]. This idea of vascular involvement is strengthened by the location of MS lesions that predominantly develop around central veins, metabolic dysfunction due to hypoperfusion, and microvascular occlusions indicating ischemic conditions [25-27]. Advanced magnetic resonance imaging techniques, including perfusion weighted imaging (PWI), have been used to better characterize and understand MS[9]. PWI techniques can be categorized into contrast and non-contrast-based techniques. Contrast based PWI techniques require the administration of gadolinium-based contrast agents (GBCA) to assess perfusion. There are two contrast based PWI methods, dynamic susceptibility contrast (DSC) and dynamic contrast enhanced (DCE). However, the use of GBCA has come under scrutiny recently with reports confirming deposition of gadolinium in the brain[16]. This is of special concern in the MS population as they undergo serial MRIs with GBCA [17]. Similarly, there are two non-contrast based PWI techniques, arterial spin labeling (ASL) and intravoxel incoherent motion (IVIM).

Previous PWI studies in MS have revealed alterations of cerebral perfusion compared with healthy controls. Acute MS lesions have shown increased perfusion when compared to normal-appearing-white-matter (NAWM)[28-30]. This hyperperfusion is thought to reflect the inflammatory process[31,32]. In contrast, PWI studies of the parenchymal tissue have reported reduced cerebral blood flow (CBF) and cerebral blood volume (CBV) in NAWM [10,11,26,32-35]. This hypoperfusion in NAWM suggests that perfusion deficits extend beyond MS lesions, and changes in perfusion may serve as a clinically relevant biomarker[10,36]. However, all of the PWI work in MS has been done in the brain leaving a gap of information in regards to perfusion changes in the spinal cord caused by the progression of MS [7]. IVIM offers an elegant non-contrast way to study the microcirculatory blood and provide in-vivo perfusion information[37]. IVIM studies have shown a good degree of correlation between IVIM perfusion metrics and physiologically and pharmaceutically induced changes in perfusion[19,20]. The IVIM technique offers two main advantages as a PWI technique[37]. First, it is a non-contrast PWI method which is of particular importance given the evidence of gadolinium retention in the brain. Second, the IVIM sequence requires a slight modification to the diffusion weighted imaging (DWI) sequence that results in only a minimal increase in scan time making the IVIM acquisition more clinically feasible. Therefore, advanced MRI techniques like IVIM that allow for the evaluation and measurement of changes in perfusion offer a great tool to gain a better understanding of MS and allow for earlier detection[9].

Proposed Methodology:

This will be a cohort study using PWI MRI to compare 20 patients diagnosed MS to 20 normal controls. MRI acquisition will focus on the cervical spinal cord as this region demonstrates a higher number of MS lesions compared to the thoracic spinal cord[7]. PWI MRI techniques can be categorized into contrast and non-contrast techniques. Contrast based PWI techniques require the administration of gadolinium-based contrast agents (GBCA). However, the use of GBCA has come under scrutiny recently with reports confirming deposition of gadolinium in the brain[16]. This is of special concern in the MS population as they undergo serial imaging with GBCA [17]. Therefore, a non-contrast PWI technique called, intravoxel incoherent motion (IVIM), will be used in this study in hopes of improving patient safety. IVIM allows for characterization of perfusion by obtaining low b-values (<200s/mm^2) during diffusion-weighted imaging as the signal attenuation at low b-values is the composite of both diffusion and perfusion[18]. Previous research has shown IVIM to be effective in multiple body parts for differentiating benign and malignant lesions[18]. IVIM also provides several other key benefits as the technique of choice by allowing simultaneous measurement of the apparent diffusion coefficient (ADC), a clinically accepted metric in differentiating MS lesions[21]. All experiments will be performed on a 3.0T whole body MR scanner in combination with a 16-channel neurovascular coil. Higher field MRI allows for a higher signal to noise ratio that is needed to improve image quality when imaging the small spinal cord[7]. IVIM acquisition of the cervical spinal cord will consist of a single-shot echo planar sequence acquiring at least three b-values ranging from 0s/mm^2 to 2500s/mm^2. Anatomical scans will also be performed including a high-resolution multi-slice multi-gradient-echo anatomical image will be acquired for lesion identification, co-registration and to serve as a reference image for post-processing segmentation. In addition, previous clinical MRI scans will be used compare radiological findings with the IVIM perfusion metrics to determine the utility of IVIM in the identification of disease progression and diagnosis. Following acquisition post-processing of the data will be performed to calculate the perfusion fraction and ADC using the simplified IVIM model[18]. A cross-sectional statistical analysis will be performed to determine significant perfusion fraction and ADC differences between the MS and normal control cohorts.

Calendar/Timeline:

Grant to be completed in 1 year.

Year 1:

June, 2020 - Receive grant funds

July, 2020 - Build and install research protocol. Begin recurrent meetings with UK collaborator

August, 2020 - Begin recruiting and scanning subjects (goal is to scan on average 1.25 subjects a week for a targeted 8 month recruitment and scanning period)

September, 2020 - Continue to actively recruit and scan subjects and recurrent meetings with UK collaborator (target: 10 scans completed total)

October, 2020 - Continue to actively recruit and scan subjects and recurrent meetings with UK collaborator (target: 15 scans completed total)

November, 2020 - Continue to actively recruit and scan subjects and recurrent meetings with UK collaborator (target: 20 scans completed total)

December, 2020 - Submit 6 month progress report. Continue to actively recruit and scan subjects and recurrent meetings with UK collaborator (target: 25 scans completed total)

January, 2021 - Continue to actively recruit and scan subjects and recurrent meetings with UK collaborator (target: 30 scans completed total)

February, 2021 - Continue to actively recruit and scan subjects and recurrent meetings with UK collaborator (target: 35 scans completed total)

March, 2021 - Finish up any remaining subject recruitment and scanning needed (target: 40 scans completed total)

Personnel:

US Researcher – (Principal Investigator): Will be responsible for all MRI scanning and data acquisition duties including: setting up MRI protocol, testing MRI protocol, participant recruitment, scanning participants, ensuring all imaging data is saved and transferred from the scanner, and uploading/sharing the data as necessary for data analysis. Perform data post-processing and analysis. Prepare manuscript for submission as well as meting presentations. Prepare 6 month and final report.

U.K. Researcher - TBD (Co-Investigator): Will help in ensuring imaging data acquires is quality checked and perform all data post-processing and analysis. Prepare manuscript for submission as well as meting presentations. Coordinate regular meetings between investigators for updates and ensure project is progressing as plan. Prepare 6 month and final report.