Report BHA-2019-01: Total-Body PET Imaging of Both Peripheral and Central Demyelination in Multiple Sclerosis*

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Abstract

Basic question: *Can a total-body PET scanner be exploited to improve evaluation, monitoring and measurement of both peripheral and central demyelination in multiple sclerosis (MS) patients?* We assume here that demyelination outside the brain may involve at least the spinal cord if not also possibly some of the larger peripheral nerves outside the spinal column in a manner that might be detected with the greater sensitivity and resolution of the Explorer PET-CT scanner.

Initial approach: Adopt a cost-effective and reduced-risk approach initially for a pilot study by using commercially available and already FDA-approved amyloid PET tracers to follow radiotracer uptake in white matter, thereby tracking demyelination versus remyelination for MS patients in comparison with normal healthy subjects. This initial approach with the Explorer total-body PET scanner used for amyloid imaging should hypothetically enable monitoring of increased versus decreased activity in both the peripheral nervous system (PNS) and the central nervous system (CNS), rather than only imaging the brain as performed in most conventional imaging evaluations for MS patients. Total-body amyloid PET imaging by the Explorer PET-CT scanner will be compared with analogous imaging by PET-MRI scanners.

Future approach: Investigate other possible radiotracers (including those not yet FDA approved) that might be useful for monitoring demyelination, neuroinflammation and/or microglial activation in both the PNS and CNS of MS patients.

Significance: Improved molecular imaging with new total-body PET scanners that provide greater sensitivity and better spatial resolution for quantitative measurement of demyelination and remyelination will support better decision-making for patient care and improved outcome measures for monitoring therapeutic drugs evaluated in clinical trials for the treatment of multiple sclerosis.

Keywords

Total-body PET scan, Explorer PET-CT scanner, PET-MRI scanner, multiple sclerosis, peripheral demyelination, amyloid imaging, inflammation imaging, microglial imaging.

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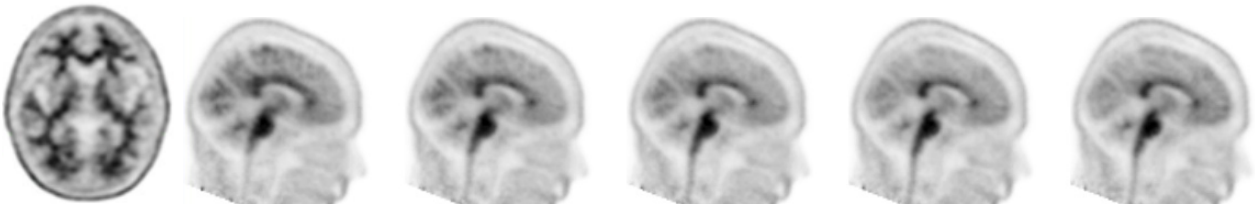
Proposed Research Project Description

Basic question: *Can a total-body positron emission tomography (PET) scanner be exploited to improve evaluation, monitoring and measurement of both peripheral and central demyelination in multiple sclerosis (MS) patients?* We assume here that demyelination outside the brain may involve at least the spinal cord if not also possibly some of the larger peripheral nerves outside the spinal column in a manner that might be detected with the greater sensitivity and resolution of the Explorer PET scanner (Cherry et al. [1]). This pilot study project description proposes an international multi-site imaging trial with collaborating partners at medical centers with operational installations of the Explorer total-body PET-CT scanner, or of a total-body PET-MRI scanner, to measure both peripheral and central demyelination in MS patients compared to normal healthy subjects.

Literature review: Demyelination in both the peripheral and central nervous systems plays a key role in the neuronal and axonal degeneration that occurs in the pathophysiology of multiple sclerosis (Lucchinetti et al. [2], Zephir et al. [3], Friese et al. [4]). To evaluate patients for the presence and severity of demyelination, magnetic resonance imaging (MRI) has been well established as the imaging modality most used in routine clinical practice (Losseff et al. [5], Thorpe et al. [6], Barkhof [7], Lycklama et al. [8], Bakshi et al. [9]). However, in recent years, molecular imaging with PET scanners has been considered as an alternative imaging modality for MS (Niccolini et al. [10], Moccia et al. [11], Moccia et al. [12]). PET metabolic and amyloid imaging has been demonstrated to be useful and safe for monitoring neurodegenerative disorders other than MS (Taswell et al. [13], Anand et al. [14], Taswell et al. [15]). However, the three radiopharmaceuticals currently approved by the US FDA for amyloid imaging (Amyvid 18F-florbetapir, NeuraCeq 18F-florbetaben, Vizamyl 18F-flutemetamol) have not yet been validated for the routine clinical evaluation of MS patients.

Most PET amyloid imaging research studies with MS patients have used Pittsburgh compound B with C11 as the radiotracer (abbreviated as [11C]-PiB PET) (Stankoff [16], Glodzik et al. [17], Veronese et al. [18], Matías-Guiu et al. [19], Bodini et al. [20], Zeydan et al. [21]) and successfully demonstrated the utility of this PET amyloid imaging agent for monitoring demyelination. As examples, Bodini et al. [22] reported that "this technique is able to quantify myelin content in multiple sclerosis (MS) lesions and to capture dynamic demyelination and remyelination over time" and Bodini et al. [23] concluded that "[11C]-PiB PET allows quantification of myelin dynamics in MS and enables stratification of patients depending on their individual remyelination potential, which significantly correlates with clinical disability. This technique should be considered to assess novel promyelinating drugs." In addition, some research studies with MS patients have demonstrated encouraging results with the use of 18F-florbetaben (Matías-Guiu et al. [24], Matías-Guiu et al. [25], Matías-Guiu et al. [26]) and 18F-florbetapir (Pietroboni et al. [27]) as the radiopharmaceuticals used for PET amyloid imaging. These images with an axial slice and a sequence of sagital slices, provided courtesy of Dr. C. Rowe (at the University of Melbourne, Australia), demonstrate



the high myelin binding of the off-target white matter uptake of 18F-flutemetamol in a PET brain scan negative for gray matter uptake of the amyloid radiotracer.

Moreover, in a recent editorial entitled "A new frontier for amyloid PET imaging: multiple sclerosis," Morbelli et al. [28] commented that "the development and clinical testing of remyelinating drugs is currently hindered by the lack of quantitative measures able to quantify remyelination reproducibly across the spectrum of MS… amyloid PET (AMY-PET) has also been suggested as a potential marker of WM damage in MS. In fact, all AMY-PET tracers bind to the WM, regardless of the presence or absence of

beta-amyloid deposition in the adjacent GM… From a clinical trial perspective, the availability of fluorinated AMY-PET tracers (with their longer halflife) already used in dementia diagnosis, may make the use of AMY-PET in tissue repair studies a realistic possibility… AMY-PET imaging in patients with MS might be a suitable tool to objectively evaluate outcome measures in proof-of-concept clinical trials as well as to validate MRI metrics of remyelination." Finally, it should be noted that none of the literature searches completed for this pilot study project description have yet found any published study on the use of PET molecular imaging agents with MS patients for both the peripheral nervous system (PNS) and central nervous system (CNS), ie, where the entire body with peripheral nerves, spinal cord and brain were all imaged simultaneously.

Initial approach: The pilot study proposes to adopt initially a cost-effective and reduced-risk approach by using commercially available and already FDA-approved amyloid PET tracers to measure radiotracer activity in white matter, thereby observing for demyelination versus remyelination in MS patients compared to normal healthy subjects. Patients with advanced MS as indicated by high disability scores and impaired motor control of extremities will be selected for the comparison with normal healthy subjects to increase the likelihood of detecting an appreciable difference in the spinal column and peripheral nerves between patients and normals. Of the three FDA-approved amyloid tracers, Vizamyl 18F-flutemetamol will be favored because it has the highest binding to myelin and uptake in white matter. This initial approach with PET amyloid imaging pursued at multiple collaborating sites with the Explorer total-body PET scanner with its dramatically improved and much greater sensitivity and resolution (Cherry et al. [1]) should hypothetically enable monitoring and measurement of increased versus decreased activity in both PNS and CNS. At other collaborating sites with PET-MRI scanners (instead of Explorer PET-CT scanners), recently published multi-modal spatial resolution enhancement methods (Grecchi et al. [29]) with the wavelet transform and statistical modeling will be applied to the image processing for the brain scans as recommended by Morbelli et al. [28]. Actual PET scanning protocols for administration of the amyloid imaging scans, whether with the Explorer PET-CT scanners or the PET-MRI scanners, will be harmonized as best possible by consensus between the cooperating collaborators at the participating sites prior to the start of the pilot study. Institutional review board (IRB) approval will be obtained from the IRB at Brain Health Alliance, and also from the IRB of any collaborating institution if required additionally by that institution. All MS patients and normal subjects participating in the research will be required to sign informed consent prior to joining the pilot study. Funds raised for the pilot study research project will be used to pay for the cost of the amyloid imaging radiopharmaceuticals and total-body imaging scans. This allocation of funds should maximize the number of subjects recruited to participate in the initial pilot study.

Future approach: If successful with results from the pilot study, the project will be continued with grant applications submitted to major funding agencies for a multi-year multi-site total-body PET imaging trial to increase the sample size and evaluate multiple serial scans for each patient instead of just a single scan per research subject. The research investigation could also study other possible radiotracers (including those not yet FDA approved) that might be useful for monitoring demyelination, neuroinflammation and/or microglial activation in both the PNS and CNS of MS patients (Matthews et al. [30]).

Significance: Improved molecular imaging with new total-body PET scanners that provide greater sensitivity and better spatial resolution for quantitative measurement of demyelination and remyelination will support better decision-making for patient care and improved outcome measures for monitoring therapeutic drugs evaluated in clinical trials for the treatment of multiple sclerosis.

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Lay Summary for Pilot Study Research Project

1. *What is the problem related to multiple sclerosis that will be addressed with this project?* Currently, there is not a good way with molecular imaging to monitor all parts of the nervous system that may show damage related to multiple sclerosis. This makes it difficult to see simultaneously where damage might be occurring in the brain, spinal cord and the nerves outside of the spinal cord. This research project will look for a new approach to viewing the damage that may be occurring in various areas throughout the body with a single scan at the imaging clinic, and to following those areas with multiple scans over time to check for either healing or worsening damage.

2. *What is the goal of this project and how does it attempt to address this problem?* The new total-body PET scanner works rapidly to take a detailed picture of the patient's whole body. By using a special imaging tracer known to bind to the white matter of the nervous system, these scans should enable us to visualize those parts of the nervous system where there is less or more myelin in the white matter with changes presumed to correlate over time with relapses and remissions in multiple sclerosis. With more detailed information and measurements from the new PET scanners, we hope to be better able to show the locations where myelin damage occurs and how it changes over time. Then we can better help patient care and monitor the success or failure of drug therapies for the treatment of multiple sclerosis.

3. *What steps will be taken during the course of this project?* For the NMSS pilot study, the first step will be to show that we can see the white matter of the brain, spinal cord, and the rest of the nervous system in detail using the special imaging tracer in normal healthy people without multiple sclerosis, and then to do similar scans for patients with severe cases of multiple sclerosis to discover whether there is a difference between the normal subjects and the MS patients. Each individual who agrees to participate in the study will have a scan done using the new Explorer PET-CT scanner or a PET-MRI scanner or both in order to compare results with the new scanners to established methods with current scanners.

4. *How is this project novel?* The Explorer PET-CT scanner provides a new way of taking image scans or pictures of the head and body simultaneously. This scanner has not been used for patients with multiple sclerosis. The special imaging tracer has not been used to follow patients with multiple sclerosis over time. However, it has been used to view the progress of other brain diseases, and it is already approved by the FDA.

5. *How and when will the results potentially impact people with MS and the scientific community?* We believe that the full study may take several years since we want to show, with serial scans over time, whether the MS disease has worsened or improved in different areas of the nervous system for each individual patient participating in the study. However, if we can show that this method will enable us to view the entire nervous system of multiple sclerosis patients, there could also be improvement and benefit to patients with initial scans done at diagnosis, both in seeing more detail of the body all at the same time and in taking less time for the patient to have the scan done for both head and body.