Clinical trials registration number: NCT02403570

Status: Patient enrolment ongoing

1 SUMMARY

Multiple sclerosis continues to be a major health problem by being the most common disabling neurological disorder of young adults, excluding post traumatic injury. In the current study, 40 patients with relapsing remitting multiple sclerosis and 40 patients with secondary progressive multiple sclerosis will undergo 2 repeated magnetic resonance imaging examinations performed one year apart each other. The aim of the study is to develop novel imaging protocols suitable for patients with multiple sclerosis using advanced magnetic resonance techniques such as rotating frame relaxation imaging. In addition, we aim to study the correlation between advanced MRI parameters and clinical disease progression.

2 INTRODUCTION

Multiple sclerosis (MS) is an autoimmune disease, where inflammation of the central nervous system (CNS) inflicts neuronal damage and permanent disability. While the treatment regime of relapsing remitting MS (RRMS) is expanding with potent therapies becoming available for clinical use, there is still no efficient treatment for secondary progressive multiple sclerosis (SPMS). According to current understanding, the progression in MS results from chronic inflammation causing diffuse demyelination, axonal injury, and neurodegeneration, which may also be fueled by oxidative stress causing mitochondrial injury (1). Extensive research effort aiming to find novel image makers has not resulted into a sensitive and accurate marker with ability to accurately characterize patients with MS. Clearly, future research is still needed to find such imaging marker.

3.1. Anatomical magnetic resonance imaging and contrast enhanced magnetic resonance imaging

Conventional magnetic resonance imaging (MRI) lesions (hyperintense on T2-weighted images, hypointense on T1-weighted images, and gadolinium enhancement) have played a major role in both research and clinical settings of MS. Furthermore, MRI has become essential to diagnosis of MS. Focal inflammatory areas are visualized as T2-hyperintense lesions in conventional MRI, but the correlation of physical disability to T2-

lesion burden is weak (2). Futhermore, areas of brain which do not display any abnormalities in T2-weigted images may demonstrate abnormal signal intensities using non-conventional MRI techniques i.e., areas of normal appearing white matter (NAWM) and gray matter (GM) could be pathologically more significant for the development of physical disability than the lesion commonly associated with MS (3). Standardized MRI diagnostic criteria for MS has been established over the last decade (4) and continue to evolve as a result of new research, improved technology and clinical experience.

3.1. Rotating frame imaging

Relaxation along a fictitious field (RAFF) is an MR imaging technique applying amplitude and frequency-modulated irradiation in a subadiabatic regime. The use of radiofrequency pulse is based on sine and cosine amplitude and frequency modulations of equal amplitudes, which give rise to a stationary fictitious magnetic field in a doubly rotating frame. The RAFF relaxation time constant (T_{RAFF}) was found to differ from laboratory frame relaxation times (T_1 and T_2) and rotating frame relaxation times ($T_{1\rho}$ and $T_{2\rho}$) (5). Rotating frame relaxations ($T_{1\rho}$ and T_{RAFF}) have shown to be quantitative MRI markers to follow up disease progression, including brain and myocardial ischemia (6) and to follow up response to therapy (7). Moreover, T_{RAFF} has shown excellent correlation with cell density in a rat glioma model, which makes it a potential biomarker to follow up therapy outcome (8). In animal model histopathologic studies a relation between T1ρ and neuronal density has been demonstrated (9, 10).

3.6. Study hypothesis

Our hypothesis is that improved non-invasive characterization of patients with MS using novel MRI techniques, including RAFF imaging, provides tools for better treatment selection and non-invasive characterizing of the disease. In addition, we hypothesize that advanced MRI could enable accurate monitoring of therapy response.

3 OBJECTIVES AND PURPOSE

Specific aims of this project are as follows:

i) To measure quantitative MR relaxation values (T_{RAFF}, T_1, T_2, $T_{1\rho}$, $T_{2\rho}$) of different brain area of patients with MS

ii) To develop and validate a novel imaging protocol suitable for MRI of MS patients

iii) To study the correlation between advanced MRI parameters with molecular and clinical markers of MS

4 STUDY DESIGN

This is an open prospective study to obtain information on applicability of rotating frame imaging techniques for the purpose of non-invasive imaging of patient with MS. The use of these novel MR imaging techniques could provide useful information about the disease microenvironment. It is hypothesized that RAFF and other rotating frame imaging techniques show non-invasively heterogeneous distribution of the disease and enable better characterization of patient with MS. Combination of rotating frame imaging techniques with other established MR methods for imaging of MS could provide non-invasive tools for the detection of disease aggressiveness. If the hypothesis is proven, advanced MRI techniques may be implemented to therapy planning as well as monitoring of therapy response.

5 PATIENT SELECTION

5.1 Source population

The MS patients in this study will be recruited from amongst the MS patients in the neurological outpatient policlinics in the Hospital Districts of Southwestern Finland and Satakunta,

5.2 Number of patients

This study comprises of two groups: patients with relapsing recurrent multiple sclerosis (Group I) and patients with secondary progressive multiple sclerosis (Group II). Both groups will include a maximum of 40 patients. In addition, a maximum of 20 patients in each group will undergo repeated MR examination in one year time period.

5.3 Inclusion criteria

- Age: 18 to 65 years old
- For Group I, the diagnosis of relapsing remitting MS made according to the Poser, McDonald's or revised McDonald's criteria before participating in the study

- For Group II, the initial MS diagnosis of relapsing remitting form of the disease according to the criteria as mentioned above, and conversion into the secondary progressive phase of the disease as evaluated by the referring neurologist according to the clinical evaluation and confirmed by the study physician.
- Mental status: Patients must be able to understand the meaning of the study
- Informed consent: The patient must sign the appropriate Ethical Committee (EC) approved informed consent documents in the presence of the designated staff

5.4 Exclusion criteria

- Any other autoimmune disease than MS requiring immunomodulatory or immunosuppressive medication
- High-dose corticosteroid treatment within 30 days before participating in the study
- Prior medical history: Patient must have no history of serious cardiovascular, liver or kidney disease
- Any psychiatric condition that compromises the subject's ability to participate in the study
- Infections: Patient must not have an uncontrolled serious infection
- No contraindications for MRI (cardiac pacemaker, intracranial clips etc)

6 MULTIMODALITY IMAGING

6.1 Pre-study evaluation

All patients are first evaluated by a study physician (neurologist or a neurology resident) Patients meeting inclusion criteria but not any exclusion criteria will be asked to participate in the study. Patients will be informed orally and in written form about the study. If they are willing to participate in the study, they will be asked to sign the informed consent form. Typically they will be allowed 2-4 days to read the patient inform sheet preferably with their close relatives before their consent to participate is requested.

7.2 Clinical evaluation

General physical examination and detailed neurological examination (expanded disability status scale, EDSS) will be performed by the study physician trained for EDSS

evaluation. A 500 meter walking test and timed 25 foot walking test (T25-FW), paced auditory serial addition test (PASAT), multiple sclerosis functional composite test (MSFC), 9-hole peg test (9-HPT) and multiple sclerosis impact scale (MSIS-29) test will be performed by a trained study nurse. These examinations will be performed within ± 4 weeks of the MR imaging

7.3 Patient preparation and positioning for imaging

The physician gives the patient a thorough explanation of the test. There is no need for fasting before MRI scanning. The patient is placed in a supine position in the MRI scanner.

7.4 MRI

The MRI examination will be performed using 3T Philips system (Philips Ingenia, Best, Netherlands) and/or 3T Philips PET/MR system (Philips Ingenuity, Best, Netherlands). No PET imaging will be done. Integrated RF coil will be used for excitation while dedicated 32 channel coil will be used for signal perception. Initially, data for anatomical sequences such as T_2-weighted turbo spin echo, FLAIR and T_1-weighted anatomic imaging in axial, sagittal and coronal directions will be acquired followed by RAFF, adiabatic $T_{1\rho}$, adiabatic $T_{2\rho}$, continues wave $T_{1\rho}$. No gadolinium-enhanced T1-weighted imaging will be performed. The overall duration of MRI examination will be about 30-40 min.

7.5 Clinical follow up

After MRI scanning the patient can return home. Treatment and follow-up will be done according to standard procedures at the Departments of Neurology.

7 ADVERSE EVENTS

The risks for the patients inflicted by participation in the study are deemed minimal. Anatomical MRI and advanced MRI techniques are considered as safe techniques because no ionizing irradiation is used. In addition, no intravenous catheters are required since no paramagnetic contrast agents will be used. The presence of claustrophobia will be evaluated in the screening phase and patients with serious symptoms will be excluded from study.

8 ETHICS

8.1 Ethical considerations

The study will be conducted in compliance with the current revision of Declaration of Helsinki guiding physicians and medical research involving human subjects (59nd World Medical Association General Assembly, Soul, Korea, 2008). MR imaging methods used in this study are non-invasive, and do not pose any health risk for the study subjects.

8.2 Ethical Review

Prior to commencement of this investigation, the study protocol, patient information sheet and informed consent form will be submitted for approval to EC of the Hospital District of Southwest Finland. The Principal Investigator (PI) is responsible for obtaining approval of the EC for the study protocol including its appendices. The PI shall file all correspondence with the EC in the Investigator`s Study File.

8.3 Potential risks and benefits to study subjects

The risks for the patient inflicted by participation in the study are deemed minimal. Both standard MRI and advanced MRI are considered as safe techniques. Though participating in the study does not provide direct medical benefit for the patient it may contribute to the development of higher quality MRI imaging in brain tumors.

9 DATA ANALYSIS

9.1 Quantitative analysis of rotating frame imaging data sets

The MR relaxation time constants for rotating frame techniques will be estimated by mono-exponential fitting of the signal intensity decays on a pixel-by-pixel basis.

9.2 Statistical analysis

All analyses will be performed with SAS version 9.1 (SAS Institute, Inc., Cary, NC). A p-value of <0.05 will be considered to be statistically significant.

10 SAMPLE SIZE

This prospective feasibility study which assesses utility of advanced MRI techniques for detection and characterization of patient with MS will enroll 80 patients. An interim analysis will be made after 15 patients with emphasis on imaging characteristics and the study may then be interrupted at the discretion of principal investigator after consulting other chief investigators if the imaging findings are found to be of no use to the patients.

11 QUALITY ASSURANCE

11.1 Training and information of study personnel

The technical and other supporting personnel of Turku PET Centre and Department of Diagnostic Radiology are well experienced in performing MRI studies. In the beginning of the study all involved personnel will be informed on the practical implementation of the protocol in a separate institutional meeting. They will be informed on the rationale of the study and possible clinical implications as well.

11.2 Protocol amendments

According to Finnish national regulations, protocol amendments can be made if all investigators agree. They are presented in a written form and dated as applicable. They include the original chapter of the study protocol and the amended chapter, with an explanation to this change. Important protocol amendments are reviewed by the local Ethical Committee.

12 STUDY SCHEDULE

The study will start in summer 2014 pending all mandatory authorizations have been obtained. All MRI studies are expected to be performed within two years. Analysis and modeling of the MRI data is feasible once 7-10 patients have been imaged. Preliminary analysis of results will be available in early 2015 and first reports are expected to be written during 2015-2016.

13 FINANCING

The study will be financed in part by Finnish Governmental Special Funding (In Finnish: ’Erityisvaltionosuus, EVO’). Additional funding is sought through national non-profit organizations such as Sigrid Juselius Foundation and Cancer Foundations of Finland.

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