Scientific title

High-resolution multi-parametric Magnetic Resonance Imaging for Focal Epilepsy

Research protocol

Version 1.1

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Scientific basis

Focal epilepsy refers to having seizures arising from a specific part of the brain[1]. In these patients, workup in magnetic resonance imaging is often necessary as patients with structural lesions have a much higher rate of seizures, ranging from 10% to 26% at 1 year and from 29% to 48% at 5 years[2,3]. However, there is also a subgroup of patients who has epilepsy not adequately controlled by anti-epileptics with unrevealing first MRI study, a dedicated MRI protocol may reveal positive lesion in 30-65% of the cases[2,4-6]. In these patients, several tricks can be applied to increase the detection rate. First, the used of a high-resolution MRI on a high-field scanner could be helpful, which can be increased the sensitivity up to 90%[7]. The use of 7T-MRI in further picking up subtle lesions in patients presenting with epilepsy has been investigated[8], further affirming the role of high resolution MRI imaging. Secondly, the use of dedicated sequences, such as T1-weighted inversion recovery sequences[9] which allow better distinction of grey and white matter, could also reveal subtle lesions such as polymicrogyria or Type 1 focal cortical dysplasia.

Our study is therefore aimed to apply the findings to the local settings, and specifically to investigate if T1-weighted inversion recovery sequences provides additional benefit in picking up more subtle lesions in patienst who had an initial first negative MRI.

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Study protocol

This study will be a prospective cohort model comparing baseline MRI and high-resolution MRI in delineation of focal abnormalities accounting for epilepsy.

Patient recruitment

Inclusion: Consecutive patients with drug-resistant focal epilepsy fulfilling the following criteria –

1. Diagnosis of focal epilepsy with a probable site identified, as defined by concordant results from any TWO of the following:
   - Clinical seminology compatible with focal epilepsy.
   - Electroencephalopathy pointing towards a specific site for focal epilepsy.
   - Postive ictal brain scintigraphy with SPECT-CT correlation.

AND

2. Previous MRI (at least one study with protocol tailored for epilepsy) which did not reveal accountable focal lesion.

AND

3. Able to consent for MRI examination (if patient under age of 18, consent for MRI will be obtained from guardian). Patients will be provided information leaflets to read on, and written consent before taking part in this study and MRI examination.

Exclusion:

- Patients who are contraindicated to magnetic resonance imaging (such as due to underlying MRI incompatible metallic implants)
- Patients who cannot cooperate for MRI scanning.
- Patients show are unable to provide informed consent.

Sample size calculation

There is no previous studies available specifically on the use of inversion recovery sequences.

Based on previous paper by deSantis et al. with use of 7T MRI the pickup rate of MRI on patients with preivous negative MRI would be around 30%. We prudently estimate that as the current MRI, the pick up rate would be lower than an even-higher resolution 7T MRI and approximately at half of previous study quoted (i.e. 15%), and a 5% false negative rate on patients who actually had lesions on previous baseline MRI. With a 80% statistical power and two-tail alpha = 0.05, approximately 22 patients who needs to have both MRI done and undergone surgery. And assuming that only 1/3 of patients who had workup will undergo surgery, approximately 66 patients are required.

MRI scanning

Patient will be scheduled to be scanned at the Siemens Prisma 3T MRI scanner at MRI facility, the Chinese University of Hong Kong. The scanning protocol consists of the following staple sequences for evaluation of focal epilepsy:

- Axial, Coronal and Sagittal (left and Right) 2D T1-weighted inversion recovery sequences focusing on site of lesion.
- 3D FLAIR T2-weighted MRI whole brain with multi-planar reconstruction (MPR).
- 3D T1-weighted Sagittal MPRAGE (Magnetization Prepared - RApid Gradient Echo) with MPR.

The following sequences will be applied optionally depending on the site of clinical suspicion and whether dedicated mapping will be required:

- Diffuse tensor imaging of whole brain (DTI)
- Functional MRI (fMRI) for mapping of specific cortical function close to the suspected site of lesion.
- Oblique coronal T2-weighted sequences of the hippocampus if suspected hippocampal sclerosis.
- Thin-cut dedicated T2-weighted or proton-density weighted images.

Contrast injection is usually not required unless otherwise clinically needed (e.g. for scanning of additional clinical inidcations).

The basic sequences will take approximately 30minutes, and the optional sequences (if needed) would be variable, the whole protocol will be completed within 1 hour.

All high-resolution MRIs performed under this study will be reported by board-certified radiologist and be available on patient's electronic health records (ePR).

Image interpretation

The baseline MRI of the patients will be retrospectively reviewed, while the MRI performed in this study will also be reviewed by two different radiologists. Radiologists are not blinded to the clinical history and site of clinical suspicion but are blinded to the subsequent surgical findings and outcomes.

The localization of the site of epilepsy will be pointed out according to a five-point confidence scale (1: very unlikely, 2: unlikely, 3: equivocal/ suspicious, 4: likely, 5: highly likely).

A likelihood score of 3 or above would indicate a positive imaging study.

Statistical analysis protocol

The primary outcome of the study is the sensitivity and specificity of the baseline MRI (bMRI) and the high-resolution MRI (hrMRI) studies, based on the standard of surgical findings on patients who underwent either intracranial EEG or surgical resection. Each of the sensitivity and specificity of the

two tiers of MRI studies (baseline MRI and high-resolution MRI) will be compared with use of contingency table and chi-square test.

The secondary outcomes would include the following:

- Number of cases with true positive, and false positive findings on bMRI or hrMRI; and descriptive statistics of findings in patients who had MRI but did not undergo surgery.
- Inter-observer and Intra-observer agreement for findings on bMRI or hrMRI by kappa statistics.

Handling and Storage of personal data

Images of MRI sequences with multiplanar reconstruction will be uploaded to patient's electronic patient records for clinical use, as well as purpose of surgical navigation planning by co-investigators performing operation. The research sequences will be stored in the database, while study images and reports will be available in the patient's electronic patient records.

All MRI scans will be stored in the picture archiving and communication system of Gerald Choa Neuroscience Center/ Prince of Wales Hospital. These images can be viewed on HA clinical workstations for the purpose of providing clinical care. Radiologist with training in Head and Neck or Neuroradiology will issue a formal radiology report regrading in the examinations, the report will be available on the ePR system.

The MRI data will be anonymized and encrypted before research analysis, which will also be done in HA clinical workstations. MRI scan data after anonymization will be stored in CUHK MRI data repository, with only non-identifiable patient particulars (age, sex, disease status) retained (informed consent obtained from patient prior to scanning). Use of selected images for publication purposes will be anticipated, patient particulars will be removed prior to exporting from HA clinical workstations.

Compliance with Guidelines of Good Clinical Practice by International conference on harmonisation of technical requirements for registration of pharmaceuticals for human use (ICH-GCP) and Declaration of Helsinki

This clinical trial is conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki, and that are consistent with GCP and the applicable regulatory requirement(s).

This trial offers additional diagnostic benefit without known added clinical risk on top of usual clinical care. The rights, safety, and well-being of the trial subjects are the most important considerations and will be prevailed in the current study. No non-clinical use of product is involved in this study. The radiological examination subjects underwent are provided by qualified medical practitioners with adequate training in radiology.

All clinical trial information should be recorded, handled, and stored in a way that allows its accurate reporting, interpretation and verification.