**Synopsis**

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| **Title:** | Magnetic Resonance Imaging (MRI) Of Brain Motion as an Indicator of Raised Intracranial Pressure. |
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## Background

Raised intracranial pressure (ICP), or intracranial hypertension, is a common problem in neurosurgical and neurological practice (1–5). The consequences of raised ICP are severely compromised brain perfusion, oxygenation and brain ischemia, and if left untreated, it can lead to brain injury, blindness, seizure, coma, stroke, or death (6). Clinical management is hampered by the lack of a reliable, non-invasive technique to determine if ICP is elevated – a suspected diagnosis of intracranial hypertension can only be confidently confirmed by invasive measurement (i.e. a pressure catheter via a burr hole or lumbar puncture). Causes of increased ICP include brain tumour; brain swelling; traumatic brain injury, obstruction to cerebrospinal fluid (CSF) flow and idiopathic intracranial hypertension (IIH). IIH is a condition that is increasing with the current epidemic of obesity (7,8). A significant cause of morbidity in young women, it is associated with a risk of blindness. The true incidence of IIH is unknown due to the difficulties in diagnosis, however, studies have estimated the annual incidence to be ~0.9/100,000 persons and 3.5/100,000 in females 15 to 44 years of age (7,9–11). The annual cost of IIH in the United States has been estimated to exceed $444M (7). At present, intracranial hypertension can only be confidently diagnosed through invasive procedures. These include: a) direct ICP monitoring which involves the placement of a pressure catheter into the cranial cavity through a burr hole; (b) an external ventricular drain placed into the lateral ventricles to monitor pressure and drain CSF; and c) lumbar puncture. MRI or CT Imaging can also reveal signs of raised ICP; however, these are often inconclusive (12). Raised ICP causes swelling of the sheath around the optic nerve (optic nerve swelling), which can be identified by optical coherence tomography (OCT). However, no consistent correlation between the level of ICP and the degree of papilledema has been established. There is a significant clinical need for non-invasive and quantitative measures of ICP. We have developed a novel method called amplified Magnetic Resonance Imaging (aMRI) (13,14), which amplifies the subtle spatial variations in cardiac-gated brain MRI scans. aMRI enhances the microscopic motion that occurs in the brain because of cardiac pulsation, enabling better visualisation and quantification of brain and arterial motion. Our team has the unique capability to investigate and model the dynamics of brain tissue, blood flow, and CSF; with experience across modulating ICP in clinically-relevant large animal models (15–18), advanced MR acquisition, and modelling.

Our recent clinical pilot data, acquired on five IIH patients, show a link between ICP and the brain’s intrinsic motion, with decreased brain motion associated with decreased ICP. This has given early evidence to our central hypothesis that the motion of the brain can be predictably and proportionally altered by changes in the level of ICP. The rationale is that this motion is strongly determined by brain compliance, which is in turn strongly affected by the overall pressure within the surrounding cranium (i.e. ICP). We also expect that compliance is affected by the level of arterial pressure and blood flow entering the cerebral vasculature. To develop robust tools for estimating ICP from brain motion measurements, we need to develop novel computational tools that accurately take all these factors into account and model the biological mechanisms to predict our MRI measurements. By incorporating our novel imaging methods, and our new computational modelling tools, we propose to develop and validate a clinically useful, non-invasive, proxy measure of ICP with the potential to revolutionise the management of patients with suspected intracranial hypertension.

### Hypothesis:

The central hypothesis posits that brain motion will be predictably and proportionally altered by changes in the level of ICP. The underlying rationale is that this motion is strongly determined by brain compliance and its perfusion, which is in turn strongly affected by the overall pressure within the cranium surrounding it (i.e. ICP).

The recent advent of amplified MRI (13,14,19,20) has resulted in improvements in our ability to rapidly observe and inspect these brain motions. aMRI amplifies the microscopic motion that occurs in the brain during a heartbeat. To test this theory, in this preliminary study, we apply aMRI pre- and post-lumbar puncture in IIH to explore whether the brain motion patterns are altered. If such cardiac-linked brain motion can be detected, this has the potential to allow for the non-invasive measurement of ICP.

### Future benefits and project aims

Utilising novel 3D amplified MRI methods and bespoke computational modelling tools, along with promising preliminary human data showing a correlation between brain motion and brain pressure, the study will investigate the functional effects of intracranial hypertension. Acquiring more data will allow for fine-tuning and translation of models to a patient population. The goal is to develop and validate a clinically useful proxy measure of ICP, permitting the non-invasive identification of patients with intracranial hypertension, with the potential to revolutionise patient management.

The action plan involves confirming the ability of their aMRI techniques and derived ICP index to detect intracranial hypertension through a clinical study of 60 patients, followed by an extension to a full clinical trial. The fact that aMRI scanning only adds ~2 minutes to a scan procedure that many patients are already undergoing means that rapid clinical uptake across MRI scanners is anticipated both throughout New Zealand and internationally.

OCT and optic nerve sheath measurements before and after the LP will allow us to correlate the quantitative measure of papilledema with aMRI and ICP. Optic nerve sheath measurements (anatomical and aMRI-derived biomechanical) will also inform currently unanswered physiological properties of this structure such as translaminar pressure differences (the difference between the intraocular pressure (IOP) and the retrolaminar tissue pressure (RLTP)) which has profound implications for both glaucoma and papilledema(16–18). In addition, we will explore why some patients have asymmetric papilledema as emerging evidence suggests a valve-like effect of the optic nerve at the optic canal (19,21)

## Study design

In this prospective study, patients with confirmed or suspected IIH will be offered the opportunity to participate. Participants will be invited to have their investigations and initial treatment performed at the Mātai Medical Research Institute, Gisborne.

MRI will be performed twice during the study and will include both standard and study-specific sequences.  The first MRI will include gadolinium-based contrast. A clinician will be present during this scan as is standard for all contrast scans. The images will be read and reported by consultant neuro-radiologists, who will signal to the research team whether proceeding to the LP is deemed safe. OCT of the optic nerve head will be acquired before and after lumbar puncture and will be reviewed by a consultant ophthalmologist.

Experienced anaesthetists will perform the LP. During this procedure, spinal manometry will be performed to record the opening and closing pressures, with the aim of achieving a closing pressure of 25 cmH2O or lower.  Furthermore, a sample of the CSF will be collected and sent to a local laboratory for routine analysis. In addition to providing a direct measure of ICP in IIH patients, LP is also used to drain CSF and temporarily lower ICP to normal, resulting in symptomatic relief.

A subsequent MRI scan will be performed within 4 hours after the LP, while ICP is low, and will allow within-subject comparison of pre-LP (high ICP) and post-LP (normal ICP) MRI features, allowing validation of the computational model.

Image acquisition:

All MRI scans will be acquired on a 3T MRI scanner (GE SIGNA Premier; General Electric, MI, USA) using an AIRTM 48-channel head coil. Cine 3D bSSFP (19) (the base acquisition for aMRI, resolution 1.2mm isotropic, 2min scan time), along with other conventional sequences (combined scan time of approximately 30 min) were acquired at baseline and post-LP. All OCT scans of the optic nerve head will be acquired with ZEISS CIRRUS 6000

## Study groups:

### Inclusion Criteria:

* Adult subject 16 years or older
* Suspected or confirmed diagnosis of IIH by consultant ophthalmologist or neurologist.
* Subject willing and able to consent.
* Documented medical history and required information available for data collection.

### Exclusion Criteria:

* Standard contraindications to MR imaging or to gadolinium-based contrast agents.
* History of lumbar spinal pathology or other vertebral pathology.

### Recruitment:

Participants will be recruited from neuro-ophthalmology clinics at Eye Institute, Auckland, and ophthalmology clinics at Greenlane Eye Clinic and Hauora Tairāwhiti. All patients who meet the inclusion and exclusion criteria will be invited to participate. Initial identification of potential participants will be done by the primary treating team. Participants will receive a brief explanation of the study by their primary treating team and a participant information sheet will be given to them. If a potential participant indicates interest in the study, their contact details will be passed on to the research team. Participants will be given time to reflect and discuss with whanau or next of kin. They will be followed up with a phone call by the co-investigators who will discuss the study further. Consent to participate in the study will be requested by the research fellows serving as co-investigators.

Participants must read, sign and date the approved consent form. Relevant data from routine clinical appointments will be reviewed by the research to ensure the participants meet the criteria.

###  Statistics

*Sample size and sample calculation rationale.*

Optical flow data, amplified with our aMRI method, show more motion with high ICP (158,200 ± 46,549) compared to controls (110,211 ± 29,301). Based on these data, a total sample size of 40 is required to achieve power > 90% (α=0.05) to show significant differences in the movement on MRI scans between the two groups. As the ICP level and reduction after LP can differ between individual cases, we have set our target group size at 50 to accommodate this variability, as well as to allow for multivariate analysis to look at the relationship between the ICP index from our model and ICP measured during lumbar puncture.

## Data collection

Demographic information:  Age, gender, ethnicity, BMI

History: previous medical history, previous ocular history, concomitant medication

Biomedical parameters: heart rate, blood pressure,

### Investigation:

1. MRI/aMRI: brain and orbit

2. LP: manometry and CSF analysis
- CSF analysis will not be collected for study. This will be sent to the primary treating team as it is clinically relevant.

3. OCT: Optic nerve head imaging

Study procedures:

* 1. OCT scan.
	2. aMRI scan, which will include both standard and experimental sequences. These images will be reviewed by a radiologist to determine if it is safe to proceed with the lumbar puncture.
	3. lumbar puncture.
	4. Four to six hours after your lumbar puncture, you will undergo a follow-up OCT scan as well as another MRI scan.

OCT scan ( 10-15 min) aMRI ( 60 mins) lumbar puncture (30 mins) 4 to 6 hour wait OCT scan ( 10-15 min) aMRI ( 60 mins)

The study visit is expected to take up to 8 hours.

Risks associated with study procedures:

Lumbar puncture:

1. Post lumbar puncture headache:
- this is the most common complication occurring in about 1 in 4 patients. It can occur due to a leak of your cerebrospinal fluid from the puncture site. The headache typically starts a few hours after the procedure however, it can start several days after the procedure. This headache typically worsens when you are sitting up and improves when you are lying down. These headaches, while typically self-limiting, can be severe and can last for weeks.
2. Nerve damage:
- this can result in short or long term pain, pins and needles or a loss of feelings in your lower limbs
3. Back pain:
- Tenderness around the puncture site may occur.
4. Infection:
- There is a risk of introducing an infection into the puncture site or meninges ( meningitis). A sterile technique is used to minimize the chances of such occurring.
5. Bleeding/haematoma:
- Bleeding in and around the spinal cord can occur causing symptoms such as severe lower back pain, pain radiating down the legs, loss of sensation in the lower area and saddle, bladder and bowel dysfunction, weakness and paralysis of the lower limbs. Rarely, this constellation of symptoms can be an indication of a condition known as Cauda Equina Syndrome, where your nerves below your spinal cord are compressed. This a medical emergency that requires prompt surgical intervention.
6. Brain herniation:
- In people with increased brain pressure due to conditions such as brain masses/ tumours, a lumbar puncture can results in a life threatening shift of brain tissue. The pre-lumbar puncture aMRI will assess for such causes. If the radiology team is not satisfied with your MRI scan we will not proceed with the lumber puncture.
7. Failure of procedure:
Sometimes it is too difficult to perform a lumbar puncture. IF this happens your primary treating team will be made aware and an alternative LP method will be provided.

Risks associated with aMRI

1. Allergic reaction to the contrast agent used to enhance the aMRI. These include but are not limited to:

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| --- | --- |
| Nausea | Swelling of the mouth and airways |
| Vomiting | Shortness of breath |
| Cardiovascular compromise | Dizziness |
| Rash | Wheeze |

1. Claustrophobia:
- Some people find being in confined spaces very challenging. The MRI machine is a narrow cylindrical tube that can induce anxiety and panic in people with claustrophobia. Please inform the research team if you are claustrophobic. They can provide additional supports and accommodations for you.

### Data visualisation and analysis:

Data analysis will correlate the ICP index from our model with the LP opening pressure through our regression model. OCT and optic nerve sheath measurements before and after the LP will be used to correlate the quantitative measure of papilledema with aMRI and ICP.

Key MRI data analysed will be 2D Phase Contrast MRI for CSF flow in the region of the cerebral aqueduct and C2 of the spine to ascertain flow rates and regurgitation fraction; 4D Blood Flow analysed through tested QVT software (4D flow analysis tool developed by associates of University of Auckland); aMRI data (Balanced Steady-State Free Precession Cine MR Imaging - cine bSSFPC MRI of the brain, amplified to 40x) to qualitatively map and quantitatively determine displacement of the brain over a cardiac cycle, with priority on areas that experience CSF flow and major brain motion, e.g. the ventricles, brainstem and upper spine.

This data will be used to generate a toolbox of normal and irregular brain patterns observed with the aim of helping with the diagnosis of brain pressure-related conditions. As such, CSF flow, Blood flow and brain displacement as measured using aMRI will be comprehensively analysed using an eclectic approach including but not limited to a principal component analysis (PCA) as well as other dynamic analysis, with the potential of building a machine-learning-based algorithm to better assist in the categorisation of various brain pressure related conditions such as IIH.

## Personal Findings, Incidental Findings and Communication Policy

If an incidental finding is discovered during the study analysis, the researcher will:

* Inform the participant of the ‘potential’ incidental finding
* Notify the Mātai clinical radiologist of relevant clinician of the incidental finding for their review.
* Update the participant on the negative results or inform the participant an incidental finding is confirmed, and they will be referred to their primary treating team or general practitioner for clinical review

If an incidental finding is confirmed:

* The relevant clinician will complete the incidental findings form and inform the participant’s primary treating team/ GP

·   The radiology senior administrator will ensure the referral for clinical assistance is sent to the GP and up-date the incidental findings database

·   The nominated primary treating team/ GP will inform the participants and recommend a suitable health professional for clinical follow-up

Furthermore, incidental findings will be communicated to the primary treating team and GP to mitigate risk of issues arising.

## Data Management:

MRI and OCT data will be de-identified, and research participation will be confidential as this is protocol. The following will be used to de-identify participants:

* All data will be stored securely for ten years as per legal requirements and therefore confidential. Raw and processed MRI data will be stored on password-protected Mātai Medical Research Institute computers, and back-ups of raw MRI (de-identified) data will be stored in a University of Auckland server, managed by the Centre for eResearch of the University of Auckland for post-processing and analysis in situ. Upon the conclusion of the project, all research data will be archived in a secure location within the University for 10 years minimum.
* REDCap (https://www.project-redcap.org/) node hosted by FMHS will be used to store all consent forms and sensitive participant data. This includes the participants’ general practitioner details, demographic data, and NHI as per the ‘incidental findings policy’ on the Mātai MRI consent form (any incidental findings found on imaging will be reported to the participant’s primary treating team and GP).
* A copy of all MRI scans will be stored on PACS (patient imaging data management system) which is the clinical gold standard. RIS (radiological information system) will store participant details, appointment schedules, and radiological reports, as per our clinical infrastructure requirements (and as an international gold standard).

## Withdrawal of subjects:

Subjects may withdraw from the study at any time without reason. Information collected until withdrawal will be used in the study. If a participant requests the withdrawal/ deletion of their data, they will be given a 2 week period after data collection to request withdrawal of the data from this study. This is to maintain the integrity of the study.. Withdrawn data will not be used or sent for future unspecified research.

## Ethical considerations

This project will be conducted under the tenants of the declaration of Helsinki. All results will be reviewed by the relevant consultant.

## Finance and insurance:

This study is funded by the Marsden Fund as well as the Health Research Council of New Zealand. Participants will be covered under the medical indemnity insurance or ACC of the respective specialists involved.

Participants from the Gisborne area will be eligible for petrol vouchers of 50 dollars. Refreshments and lunch will be provided. The study visit is expected to take 8 hours.

Participants from Auckland will have all study related travel in Gisborne, including flights to Gisborne and accommodation covered.Additionally, a $150 koha/ allowance will be provided to cover food and other expenses. If a participants stay in Gisborne is extended due to study-related processes, the institute will also cover any additional food, accommodation, and travel costs. Participants will be informed to 48 hours of their time for the study visit, although the research team will endeavour to have them back in Auckland within 24 hours.

Ownership Rights:

Information from this study may lead to discoveries and inventions or the development of a commercial product. The rights to these will belong to the University of Auckland and Matai Medical Research Institute.

## Reporting and dissemination:

Once data is collected and analysed a report will be submitted to international peer review journals for publication for a series of articles based upon the findings of this study. Findings will also be presented at national and international conferences.

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