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The relevance of evolving grey and white matter pathology to the development of neurodegeneration and disability in multiple sclerosis

Submission date
29/06/2022

Recruitment status
No longer recruiting

Registration date
09/09/2022

Overall study status
Completed

Last Edited
09/09/2022

Condition category
Nervous System Diseases

[_] Prospectively registered
[X] Protocol
[_] Statistical analysis plan
[_] Results
[_] Individual participant data
[_] Record updated in last year

Plain English summary of protocol

Background and study aims
About 130,000 people in the UK have multiple sclerosis (MS) and, other than head injuries, it is the commonest cause of neurological disability in young adults. MS is highly variable and unpredictable: some people with MS develop few neurological problems over decades, while others develop significant progressive disability. Overall, it is thought that the loss of nerve cells determines irreversible disability in MS, but we do not know what the main cause of nerve cell damage is. On magnetic resonance imaging (MRI) scans the most obvious sign of MS is the presence of lesions in brain white matter, and nearly all people with MS have an MRI scan looking for these lesions to help establish a diagnosis. However, these lesions appear to explain only a small amount of overall disability and nerve damage due to MS.

About a decade ago we undertook a research study investigating grey matter (the part of the brain which contains nerve cells) abnormalities in MS. The study provided much-needed insights into previously overlooked aspects of MS, and in particular, highlighted that grey matter changes in some people with MS could be substantial and associated with neurological function, memory, and thinking. Practically, it has led to at least one new MRI method being used in trials of treatments for MS.

Building on our previous study, we now aim to see if any of the MRI scan measures we previously looked at can predict how people with MS are now, and how these MRI features have changed over a decade. We hope that this work will help us to identify targets for treatment long before they have had a chance to cause disability.

Who can participate?
Adult patients with MS and healthy adults with no known neurological disease who were included in the original research study will be invited to participate in the study.

What does the study involve?
The study will follow up a cohort of patients with MS from the original research study, a little over a decade after their initial assessments. The study will involve a single visit to the UCL Queen Square Institute of Neurology, London, or, if some participants are unable to attend the UCL Institute of Neurology, a brief medical interview will be conducted by telephone to evaluate their disease status and current levels of disability.
During the visit, the participants will complete a 30-minute clinical assessment (30 min) which will include the collection of a brief medical history, a neurological examination, a walking assessment, and tests of walking speed, upper limb function, attention, and speed of information processing. There will also be a
15-minute cognitive assessment, to measure attention and speed of information processing, verbal memory immediate recall, and visual memory immediate recall. Participants will also have an MRI scan which will take around 90 minutes.

What are the possible benefits and risks of participating?
This study will not directly affect participant care or treatment. We hope that participants will be able to learn more about current MS research and will also gain some satisfaction from knowing that they are helping with research that may eventually contribute towards the development of better treatments for MS.

There are only minor risks to participants associated with this study. MRI is a safe imaging technology which uses a strong magnetic field and radio waves to create images of part of the inside of the body. There is no ionising radiation (such as X-rays) involved in MRI. Some people may feel a little claustrophobic when they are in the scanner, however participants will always be able to speak to the person controlling the scanner via an intercom, and they will stop the scanning session at any time if you ask them to do so. Participants will also have a buzzer that they can squeeze to attract attention. Very occasionally during scans people also experience a mild tingling or twitching feeling in their body, arms, or legs. This is harmless, but if it happens and causes participants any distress, participants can ask for the scanning session to be stopped.

Where is the study run from?
University College London (UK)

When is the study starting and how long is it expected to run for?
From May 2021 to May 2025

Who is funding the study?
Medical Research Council (UK)

Who is the main contact?
Dr Nitin Sahi, n.sahi@ucl.ac.uk

Contact information

Type(s)
Scientific

Contact name
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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
310565

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
IRAS 310565, CPMS 52645, Grant Codes: MR/W019906/1

Study information

Scientific Title
The dynamics and clinical relevance of grey matter and periventricular white matter pathology in multiple sclerosis

Acronym
GML03

Study objectives
1. Cortical grey matter atrophy is essentially unrelated to grey matter lesion formation
2. White matter tract-mediated abnormalities lead to regional grey matter atrophy
3. Gradients in cortical grey and periventricular white matter abnormalities predict future cortical atrophy
4. Iron deposition and hypo-perfusion promote cortical atrophy
5. Grey matter compared with white matter MRI features better predict a transition from relapsing-remitting to secondary progressive MS and better predict disability accrual
6. Early gradients in cortical grey matter and periventricular white matter abnormalities predict a transition from relapsing-remitting to secondary progressive MS, and disability accrual, and do so independently of grey matter and white matter lesions

Ethics approval required
Old ethics approval format

Ethics approval(s)

Approved 24/05/2022, NHS/HRA London - Queen Square Research Ethics Committee (HRA NRES Centre Bristol, 3rd floor, Block B, Whitefriars, Lewins Mead, Bristol BS1 2NT; +44 (0)2071048225, +44 (0)2071048284; queensquare.rec@hra.nhs.uk), ref 22/PR/0410

Study design
Observational cohort study

Primary study design
Observational

Study type(s)
Other

Health condition(s) or problem(s) studied
Multiple Sclerosis

Interventions
We plan to follow up a cohort of patients with Multiple Sclerosis (MS), clinically isolated syndrome (CIS), and healthy controls for a little over a decade after their initial assessments, n=140 out of 209 (We originally recruited 148 people with MS [69 with Relapsing Remitting MS (RRMS), 48 with Secondary Progressive MS (SPMS), and 31 with Primary Progressive MS (PPMS)], 9 with a CIS, and 52 healthy controls). The study will involve a single visit to the UCL Queen Square Institute of Neurology, London. After obtaining informed consent the participants will complete the following assessments during the visit:
1. Clinical assessment (30 min):
1.1. Brief medical history
1.2. Neurological examination
1.3. Expanded Disability Status Scale (EDSS) assessment scored using the results of the neurological exam and a walking assessment
1.4. Multiple Sclerosis Functional Composite Scale (MSFC) based on a test of walking speed, a 9-hole peg test for upper limb function and the Paced Auditory Serial Addition Test (PASAT) which measures attention and speed of information processing
2. Brief International Cognitive Assessment for MS (BICAMS) (15 min) which includes the Symbol Digit Modalities Test (SDMT) which measures attention and speed of information processing, the California Verbal Learning Test (verbal memory immediate recall), and the Brief Visuospatial Memory Test (visual memory immediate recall).
3. MRI scanning (90 min). A combination of standard and novel MRI techniques will be used, including proton density/T2/FLAIR, PSIR sequences, 3D T1 weighted imaging, magnetisation transfer ratio (MTR) imaging, diffusion-weighted imaging (DWI), macromolecular tissue volume (MTV), quantative susceptibility mapping (QSM), and arterial spin labelling (ASL).

Some participants may wish to be part of the study but be unable to attend the UCL Institute of Neurology. In this situation, after obtaining consent a brief medical interview will be conducted by telephone to evaluate disease status and current levels of disability.

Intervention Type
Other

Primary outcome(s)
1. Cortical grey matter atrophy measured using 3D T1-weighted volumetric MRI scans at the single study visit

2. Transition to secondary progressive MS measured using clinical assessment based on history and examination at the single study visit
3. Disability accrual measured using the Expanded Disability Status Scale (EDSS), Multiple Sclerosis Functional Composite (MSFC), and cognitive measures at the single study visit

Key secondary outcome(s))
There are no secondary outcome measures

Completion date
04/05/2025

Eligibility

Key inclusion criteria
1. Included in the original research study (ref: 917/09).
2. Aged 18-65 years (at time of original study)
3. Able to undertake written informed consent in English
4. Diagnosis of clinically definite MS or were healthy controls with no known neurological disease

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Upper age limit
65 years

Sex
All

Key exclusion criteria
1. Involvement in other research studies or medical interventions which might have contraindications for this study
2. Neurological disease other than CIS and MS that impedes study interpretation
3. Contraindication to MRI scanning is not an exclusion criteria for the study, however participants must meet safety criteria to take part in this element of the study. Participants will be asked to complete the NMR Research Unit’s MRI safety checklist to determine whether or not it is safe to proceed with MRI scanning.

Date of first enrolment
01/05/2022

Date of final enrolment

31/01/2025

Locations

Countries of recruitment
United Kingdom

Study participating centre
UCL Queen Square Institute of Neurology
Queen Square
London
United Kingdom
WC1N 3BG

Sponsor information

Organisation
University College London

ROR
https://ror.org/02jx3x895

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

Alternative Name(s)
Medical Research Council (United Kingdom), UK Medical Research Council, Medical Research Committee and Advisory Council, MRC

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Individual participant data (IPD) sharing plan

The datasets generated during and/or analysed during the current study are/will be available upon request from the Principle Investigator (Declan Chard, d.chard@ucl.ac.uk).
We will collect demographic, clinical assessment (including neurological and cognitive test score), and MRI data. Data will only be available from participants who have consented for their data to be shared anonymously or pseudo-anonymously with other researchers.
Where needed, data sharing will be authorised by the Principal Investigator (or their successor) for this study. Data sharing agreements are subject to review by UCL Business (https://www.uclb.com/for-researchers/material-transfer-agreements/). Data sharing is subject to the UCL Information Security Policy (https://www.ucl.ac.uk/information-security/informationsecurity-policy).

IPD sharing plan summary

Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No
Protocol file	version 2.0	10/05/2022	16/08/2022	No	No