ISRCTN47912798 https://doi.org/10.1186/ISRCTN47912798

Brain complications of COVID-19 in hospitalised patients and its consequences

Submission date	Recruitment status	[X] Prospectively registered
04/01/2021	No longer recruiting	[ ] Protocol
Registration date	**Overall study status**	[ ] Statistical analysis plan
04/01/2021	Completed	[ ] Results
Last Edited	**Condition category**	[ ] Individual participant data
04/01/2021	Nervous System Diseases	[ ] Record updated in last year

Plain English summary of protocol

Background and study aims
COVID-19 patients frequently suffer brain problems during the infection and can be left with symptoms of brain injury. Similar problems have been seen in previous pandemics, including Spanish influenza over 100 years ago, but how and why this occurs is poorly understood.

The study will investigate the questions: in whom does COVID-19 cause injury? Does it do this by invading the brain? Or by triggering excessive immune responses or interfering with the blood supply to nervous tissue?

This study is a unique opportunity to understand how these problems occur and develop strategies to prevent and treat them.

Who can participate?
Adults admitted to a UK hospital during the COVID-19 pandemic suffering from both COVID-19 (by WHO criteria) and an acute neurological/psychiatric complication. The study team have been notified of 800 UK patients with these complications due to COVID-19. 500 control patients who had COVID-19 or other severe infections but did not develop brain complications will also be recruited. Participants will also be recruited prospectively in subsequent waves of infection.

What does the study involve?
The study team will conduct an in depth clinical, laboratory, and imaging study. The study will evaluate symptoms, signs, and brain function during hospitalisation and at follow-up (at 3 to 9 months). The study team will assess markers of brain injury, inflammation, and brain scan changes in these patients.

What are the possible benefits and risks of participating?
This study will be used to determine whether anti-viral medication, or treatments that modulate the immune system, or that improve blood supply, will help, and if so, in which patients.

This understanding will be applied through the COVID-Neuro Coalition Clinical Care Task Force to develop clinical care guidelines, identify patients for targeted clinical trials, and ultimately improve patient outcomes.

Where is the study run from?
Cambridge University Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
From October 2020 to April 2022

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

Who is the main contact?
Dr Benedict Michael (Liverpool) and Prof Gerome Breen (KCL)
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Study website
http://covid-cns.org/

Contact information

Type(s)
Scientific

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil Known

Secondary identifying numbers
MRC: MR/V03605X/1

Study information

Scientific Title
Neurological and psychiatric complications of COVID-19 in hospitalised patients and the neurological, psychiatric and cognitive sequelae: the COVID-19 Clinical Neuroscience Study (COVID-CNS)

Acronym
COVID-CNS

Study objectives
1. Excluding recognised causes (e.g. hypoxia, medication), hospitalised COVID-19 patients who develop acute neurological complications are younger, have an abnormal Glasgow coma score on admission, and higher serum markers of inflammation, than hospitalised controls with /without COVID-19; and these patients have a worse medium-term neurological, cognitive and psychiatric outcome.
2. Hospitalised COVID-19 patients who develop acute neurological complications have a dysregulated pro-inflammatory immune response, driven by IL-1 and IL-6 rather than direct viral CNS infection.
3. Acute neurological complications are associated with an acute increase in serum markers of CNS injury and these markers in both acute and post-acute serum predict later sequelae. In some patients, new neurological complications later emerge or re-emerge in those with biomarker evidence of CNS injury or the development of antineuronal antibodies 12.
4. Similar, but milder neurological symptoms are reported in the community population who have had COVID-19 and are predicted by polygenic scores. If these scores are combined with CNS injury and inflammation markers they more accurately predict acute neurological complications of COVID-19.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Pending 08/01/2021, ethical amendment to NIHR BioResource ethical approval (submission 8.1.21)

Study design
Multi-centre longitudinal case-control study

Primary study design
Observational

Secondary study design
Case-control study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a participant information sheet: covidcns@liverpool.ac.uk

Health condition(s) or problem(s) studied
Acute brain complications of COVID-19 and their neurological, psychiatric, and cognitive sequelae

Interventions
The study team have characterised the basic clinical details of 800 patients currently/recently hospitalised with COVID-19 with neurological complications from the CoroNerve and ISARIC -4 C's studies. CoroNerve n=400, and ISARIC-4C's n=400. 400 controls will be recruited form the ISARIC-4C's trial and a further 100 will be recruited. Based on current data, approximately 20-30% will currently be hospitalised at initial data collection. Prospective participants will be recruited in subsequent waves of infection. All patients will be consented into existing NIHR BioResource infrastructure for long-term sustainability of follow-up.

Baseline assessment at admission will comprise of;
1. Acute Clinical Case Notes Review of Neurological Complications
2. Baseline data for demographics (including black and minority ethnicity background) and the index episode of acute neurological complication of COVID and previous history of neurological disorder, obtained by the Clinical Research Network (CRN) Nurses, supported by the study team:
2.1. Using the Brain Infections UK Case Record Form, from clinical case notes and routine test results
2.2. Neuroimaging files (estimated in 40-50% of cases, as CoroNerve over-represents patients under Neurologists and in large Neuroscience Units)
2.3. Retained serum (ISARIC-4C's and local) and CSF (Co-I's Neuroscience BioBanks)

Follow-up data will be obtained by face-to-face assessment at 3-9 months post-discharge for:
1. Neurology: Liverpool Brain Infectious Outcome Score and Neurological Impairment Scale mapped against functional outcomes.
2. Cognitive/psychiatric:
2.1. CNS-NeuroCog Protocol (built on UK BioBank, the MOCA/MMSE, CAMCOG, and CANTAB tools; piloted on 50).
2.2. NIHR BioResource COPING Protocol (an extended UK Biobank questionnaire covering neurological, cognitive, and psychiatry symptoms, already completed in >30,000).
3. Neuroimaging
4. Brain structural and functional connectivity changes will be measured by MRI in acute and post-infectious cases (compared to controls) and will be related both to blood immune and brain injury markers, and to distinct clinical phenotypes, thus providing a crucial explanatory link between biology and clinical features.

Intervention Type
Other

Primary outcome measure
1. Neuroglial injury markers (including Tau, NfL, GFAP, S100, and NSE) measured using quantitative analysis of plasma at baseline (admission) and follow-up (at 3 to 9 months post-discharge)

Secondary outcome measures

1. Cytokine/chemokine profiles measured by luminex from samples at baseline and follow-up
2. Volume of T2 FLAIR signal measured from brain magnetic resonance imaging at baseline and follow-up

Overall study start date
31/10/2020

Completion date
30/04/2022

Eligibility

Key inclusion criteria
Cases and controls:
1. Aged >17 years
2. Admitted to a UK hospital during the COVID-19 pandemic
3. Suffering from COVID-19 (by WHO definitions. 'Confirmed': Positive PCR of respiratory samples or serology and 'Probable' by chest radiograph/CT evidence of COVID-19 but PCR /serology negative or not tested)

Cases only
1. Suffering from an acute neurological/psychiatric complication (e.g. encephalitis, unexplained [e.g. non-hypoxic] encephalopathy/delirium, and stroke without major risk factors).

Participant type(s)
Patient

Age group
Adult

Sex
Both

Target number of participants
1,400

Key exclusion criteria
Does not meet inclusion criteria

Date of first enrolment
01/02/2021

Date of final enrolment
30/04/2022

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
University of Liverpool
West Derby Street
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Study participating centre
King's College London
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WC2R 2LS

Study participating centre
Cambridge University
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Sponsor information

Organisation
Cambridge University Hospitals NHS Foundation Trust

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Sponsor type
Hospital/treatment centre

Website
http://www.cuh.org.uk/

ROR
https://ror.org/04v54gj93

Funder(s)

Funder type
Government

Funder Name
Medical Research Council

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

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
UK Research and Innovation

Alternative Name(s)
UKRI

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Funder Name
National Institute for Health Research

Alternative Name(s)

National Institute for Health Research, NIHR Research, NIHRresearch, NIHR - National Institute for Health Research, NIHR (The National Institute for Health and Care Research), NIHR

Funding Body Type
Government organisation

Funding Body Subtype
National government

Location
United Kingdom

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal. Raw data for proteomic and immunological data will be made available, upon publication in existing open access repositories as required by the WHO and ICMJE.

Intention to publish date
30/04/2022

Individual participant data (IPD) sharing plan
The data sharing plans for the current study are unknown and will be made available at a later date.

IPD sharing plan summary
Data sharing statement to be made available at a later date