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An investigation of biomarkers in acute stroke

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Registration date 17/06/2024	**Overall study status** Ongoing	[ ] Statistical analysis plan [ ] Results
Last Edited 02/07/2024	**Condition category** Circulatory System	[ ] Individual participant data [ ] Record updated in last year

Plain English summary of protocol

Background and study aims
Stroke is responsible for 10% of all deaths in the UK and represents a leading cause of adult disability. Stroke has a massive emotional and financial impact on families and places a huge burden on the economy, with a projected future cost of £26 billion. One of the biggest challenges in stroke treatment is accurate and fast diagnosis, which influences subsequent treatment and reduces the extent of irreversible brain damage. This study aims to assess the relationship between a panel of blood, saliva and urine biomarkers in patients presenting with acute stroke, and compare this to patients presenting with 'stroke mimics' (non-stroke conditions which present as stroke, such as low blood glucose) to determine whether it is possible to differentiate between these conditions.

Who can participate?
Patients over the age of 18 years old with a suspected stroke who are transferred to Queen Elizabeth Hospital Birmingham (QEHB) for further assessment and treatment.

What does the study involve?
Patients presenting with suspected stroke to the QEHB will be assessed for eligibility at the time of initial contact with a paramedic, and where consent is obtained from the patient or their proxy, blood and salivary biomarker tests will be taken. This will be followed by blood, saliva and urinary biomarker testing at 6 subsequent time points in the patient's hospital stay (4-12 hours post-injury; 24 hours post-injury; 48 hours post-injury; day of discharge from hospital) as well as three further points after discharge (day 90, day 180 and day 365). In addition, where this would be part of clinical care, cerebrospinal fluid (the fluid which circulates the brain and spine) and cerebral microdialysis (which monitors internal brain chemistry) will also be obtained. Moreover, magnetic resonance imaging (MRI) will be obtained at three time points: within the first 30 days; day 180 and day 365.

What are the possible benefits and risks of participating?
The benefits for participants as individuals are small, although they will have additional tests and possibly scans not enough is yet known about these to substantially change their treatment. Although there will not be any benefits to the participant's treatment, this work will help to develop ways to improve diagnosis and treatment for patients with stroke in the future.

The risks of participation are small. Where blood tests are required, the risks are identical to normal clinical tests. MRI scans are not known to have any adverse effects, although they involve lying still for a prolonged period of around 40 minutes which may be uncomfortable.

Where is the study run from?
1. QEHB (UK)
2. University of Birmingham (UK)

When is the study starting and how long is it expected to run for?
June 2023 to May 2026

Who is funding the study?
The Stroke Association

Who is the main contact?
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2. Dr Mark Willmot, mark.willmot@nhs.net
3. Dr Sheikh Momin, s.m.b.momin@bham.ac.uk

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
125988

Protocol serial number
RG_13-164, IRAS 125988, CPMS 63160

Study information

Scientific Title
Golden Hour for Stroke (GHoSt): a prospective study of biomarkers for acute stroke

Acronym
GHoSt

Study objectives
Biomarkers of acute stroke may have diagnostic capability in differentiating between stroke from 'stroke mimics' in the acute stage, which may accelerate subsequent investigation and treatment of stroke. Moreover, such biomarkers may provide prognostic information for an individual patient to inform acute and sub-acute treatment stratification and future prognosis. This study aims to investigate a panel of biomarkers to assess prognostic accuracy in comparison to standard hospital investigations (laboratory tests and imaging) and outcome measures at 3, 6 and 12 months.

Objectives:
1. To assess the differences in biomarker profile amongst patients with confirmed stroke and 'stroke mimics' in the first 48 hours post-onset of symptoms
2. To assess the prognostic capability of biomarkers in functional and quality of life outcomes in stroke at 3, 6 and 12 months.

Ethics approval required
Ethics approval required

Ethics approval(s)
approved 05/02/2024, Wales Research Ethics Committee 5 - Bangor (Health and Care Research Wales, Castlebridge 5, Cardiff, CF11 9AB, United Kingdom; +44 (0)2922 940910; Wales.REC5@wales.nhs.uk), ref: 13/WA/0399

Study design
Multicentre observational longitudinal single-blinded cohort study

Primary study design
Observational

Study type(s)
Diagnostic, Efficacy

Health condition(s) or problem(s) studied
Stroke

Interventions
Patients with suspected stroke who meet the inclusion criteria will be recruited to undergo additional serum, urine and saliva sampling but otherwise will receive standard care and investigations as per current local ambulance and hospital clinical protocols.

The following samples will be taken:

Blood
Sampling of blood will be performed at regular intervals as outlined in the additional files. During emergency treatment at the point of first contact with the health professional, venous access may be gained to allow the delivery of drugs and fluids. At this timepoint, blood samples are not usually withdrawn as there are currently no clinical investigations available. The study proposes to withdraw 28 ml of blood for early biomarker analysis at this point. The initial sample may be taken by the paramedic team at the scene or by the nursing team in the hospital. Blood samples are taken routinely over the following days of admission to monitor various factors, where feasible research samples will be withdrawn alongside clinical samples.

Urine
Urine is an important source of epigenetic and peptide biomarkers which have demonstrated significant utility in predicting the scale of injury burden and may have the potential to forecast outcomes in the trauma patient population. The team propose to collect 50 ml of urine for biomarker analysis at the timepoints outlined.

Saliva
Sampling of saliva via mouth swabs will be performed at the timepoints outlined. It is proposed to collect one swab per time point for biomarker analysis. The initial sample may be taken by the paramedic team at the scene or by the nursing team in the hospital.

Imaging
It is intended that all participants in this study will undergo at least one brain-imaging test as part of routine care. The outcomes of these tests (e.g. CT/MRI) will also be recorded as part of the study.

Biomarker analysis
Blood, urine and saliva will initially undergo next-generation sequencing (NGS) to generate a biomarker array. There are two main categories of biomarkers in this study: first, a prespecified assay of biomarkers associated with brain injury will be analysed: S100B, glial fibrillary acidic protein (GFAP), myelin basic protein (MBP), neurofilament-light (NFL) and N-Acetylaspartic acid (NAA). Secondly, a Benjamini-Hochberg correction for multiple comparisons at a false discovery rate < 0.05 will be applied to identify candidate biomarkers for further laboratory analysis, using techniques such as chemiluminescent assays and real time PCR. Moreover, exploratory microparticle and metabolomic analyses will also be conducted. These techniques will allow the biomarker to be quantified at each timepoint defined, enabling comparisons of biomarker level in stroke and stroke mimic patients (Primary Outcome 1) and biomarker level and functional outcome (Secondary Outcome 3).

Genetic analysis
Mitochrondrial DNA (mtDNA) haplogroups will be analysed using PCR to determine any correlations with functional outcomes. Genetic analysis will be performed initially looking at susceptibility or protective factors with differing mtDNA haplogroups. Regarding genetic analysis for mtDNA haplogroups, the research team will be specifically looking at variations within the common European groups including H, J, K, T, and U.

Sampling – Urine
Sampling of urine will be performed at regular intervals from admission to the hospital through to 12 months post-injury. The team propose to collect 50 ml of urine for biomarker analysis. Urine is an important source of epigenetic and peptide biomarkers which have demonstrated significant utility in predicting the scale of injury burden and may have the potential to forecast outcomes in the trauma patient population.

Saliva
Sampling of saliva via mouth swabs will be performed at regular intervals from the time of injury through to 12 months post-injury. It is proposed to collect one swab per time point for biomarker analysis. The initial sample may be taken by the paramedic team at the scene or by the nursing team in the hospital.

Microdialysis
Intracranial pressure monitoring and more recently microdialysis catheter monitoring are part of routine clinical care for head trauma allowing monitoring of intracranial pressure and brain oxygen tension; important clinical variables. Microdialysis is a technique that involves the placement of a catheter containing a semi-permeable membrane into a tissue. A fluid is then circulated over this membrane and small-molecule substances in the tissue will then diffuse across the membrane allowing analysis to be performed to detect those of interest, this fluid is known as a dialysate. Although this technique was first developed 50 years ago it has only recently been adopted into routine clinical practice in certain centers. Presently the dialysate is discarded following bedside measurement of oxygen, however, this fluid could provide a wealth of potential biomarkers, it is therefore proposed to recover the fluid for analysis. Control patients would not be expected to have intracranial pressure monitors or microdialysis catheters as these are solely used in the setting of neurosurgical problems. Catheter placement will be dictated by clinical need.

Cerebrospinal fluid (CSF)
CSF samples may be withdrawn as part of routine clinical management, particularly where extra-ventricular drains or similar have been placed. Where this happens, an additional sample will be withdrawn for analysis.

Imaging
It is intended that all participants in this study will undergo at least one brain-imaging test as part of routine care. According to clinical indications, some participants will undergo further imaging investigations. In addition, an imaging sub-study will be performed on a random selection of patients as detailed below. MRI, MRS, and DTI sequences will be attained. The initial scans will be interpreted using the imaging findings as biomarkers for ABI. Specifically structural and micro-haemorrhages on MRI, N-acetyl aspartate (NAA), choline, creatinine, myoinositol with magnetic resonance spectroscopy and changes in fractional anisotropy with diffusion tensor imaging as a marker of axonal disruption.

Cognitive and psychological questionnaires
The complexity of the brain leads to a wide array of effects following injury. A plethora of tests have been developed to try to capture these and relate them to the severity of injury.

This study is part of the wider 'Golden Hour' cohort study including patients with traumatic brain injury, who will also undergo testing for the same biomarkers at the same timepoints.

Intervention Type
Procedure/Surgery

Primary outcome(s)
1. Sensitivity, specificity, negative predictive value, positive predictive value, area under receiver operating curve (ROC) for individual components and a combined diagnostic panel of serum, urine and saliva biomarkers (as outlined in the Interventions section) to differentiate between stroke and stroke mimics at the time of first contact with a healthcare professional up to 24

hours post-suspected stroke
2. Functional status measured using the modified Rankin Scale at 3 months

Key secondary outcome(s))
1. Functional outcome measured using the EuroQol health-related quality of life (EQ-5D-5L) and the Quality of Life after Brain Injury (QOLIBRI patient-reported outcomes) scales at 6 and 12 months
2. Mental health status measured using the Patient Health Questionnaire-9 (PHQ-9) for depression and Generalised Anxiety Disorder Assessment (GAD-7) for anxiety at 6 and 12 months
3. Exploratory analysis of the correlation between serum, salivary and urine biomarkers measured using magnetic resonance spectroscopy (MRS) at 3, 6 and 12 months

Completion date
31/05/2026

Eligibility

Key inclusion criteria
Study group: Patients who have suffered an acute brain injury from confirmed stroke resulting in presentation to University Hospitals Birmingham

Control group: Patients with a 'stroke mimic' (an alternative diagnosis presenting as stroke); non-head trauma patients

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Key exclusion criteria
Study group: patients under 18 years of age; patients with devastating injury who are unlikely to survive >24 hours

Control group: patients under 18 years of age; patients with a recent head injury or known neurological condition; patients with a devastating injury who are unlikely to survive >24 hours

Date of first enrolment
01/05/2024

Date of final enrolment

31/05/2026

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
University Hospitals Birmingham NHS Foundation Trust
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Study participating centre
West Midlands Ambulance Service NHS Trust
Millenium Point
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Sponsor information

Organisation
University of Birmingham

ROR
https://ror.org/03x94j517

Funder(s)

Funder type
Charity

Funder Name
Stroke Association

Alternative Name(s)
TheStrokeAssociation, TheStrokeAssoc

Funding Body Type
Private sector organisation

Funding Body Subtype
Associations and societies (private and public)

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 Dr Sheikh Momin, s.m.b.momin@bham.ac.uk.

All data will be processed and stored in accordance with the Data Protection Act (2018) and General Data Protection Regulations (GDPR). Patient data will be stored securely on UHB servers and pseudonymized data will be recorded on the RedCap database owned by UoB. Access to this data will be restricted as stated on the Patient Information Sheet (PIS).

IPD sharing plan summary
Available on request

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Participant information sheet	version 3.0	02/11/2023	29/04/2024	No	Yes
Participant information sheet	version 3.0	31/07/2023	29/04/2024	No	Yes
Participant information sheet	version 3.0	31/07/2023	29/04/2024	No	Yes