ISRCTN14305388 https://doi.org/10.1186/ISRCTN14305388

The gait in idiopathic normal pressure hydrocephalus study

Submission date	Recruitment status	[X] Prospectively registered
24/11/2022	No longer recruiting	[X] Protocol
Registration date	**Overall study status**	[_] Statistical analysis plan
08/12/2022	Completed	[_] Results
Last Edited	**Condition category**	[_] Individual participant data
16/06/2025	Nervous System Diseases	[X] Record updated in last year

Plain English summary of protocol

Background and study aims

Idiopathic normal pressure hydrocephalus (iNPH) is a condition causing a progressive decline of gait, bladder and cognition. The decline in gait in particular can be improved with the drainage of cerebrospinal fluid (CSF) in many patients. To determine which patients are likely to benefit, CSF is temporarily drained during a lumbar puncture (LP, “tap test” or TT). Demonstrating improvement in patients’ mobility after TT is crucial to identify which patients should be offered permanent treatment correctly. Current practice relies on manual mobility assessments. Changes can be difficult to detect if gait is only mildly impaired or if the change is discrete. Video-recorded gait performance is often used. There is no universally accepted, standardized rating system. The test is often rated as “equivocal” or "no improvement" and people with iNPH (pwN) are consequently denied treatment. Few studies have used advanced gait analysis techniques in pwN - none has reported analyses which include joint kinetics and kinematics. A more sensitive method to identify changes in mobility in pwN is needed. This work will be the first to characterise gait impairment in pwN compared to healthy controls (HC) using 3-dimensional gait analysis (3D), quantify changes after LP in gait in reference to clinical assessments, and explore thresholds to differentiate responders from non-responders to LP compared to clinical assessments with the aim of providing an objective reliable primary outcome variable for future randomized controlled clinical trials and to improve clinical care. The outcomes of this work will inform clinical care guidelines and research into better diagnosis and treatment of pwN.

Who can participate?

Patients with probable NPH who are awaiting LP and healthy control participants at approximately the same age. pwN will be recruited from the regional NPH clinic at Salford Royal Hospital (SRH) where they will undergo TT and HC from the general public.

What does the study involve?

The study involves 3D gait analysis before and 24 hours after LP in NPH patients. Healthy control participants are only assessed once.

What are the possible benefits and risks of participating?

There are no direct benefits for trial participants. Equally, there are no risks.

Where is the study run from?
Northern Care Alliance (UK), Clinical scientific oversight is provided by our partners at Gothenburg University (GU), and 3D will be conducted at the Manchester Metropolitan University (MMU) (UK)

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

Who is funding the study?
1. Hydrocephalus Association (USA)
2. National Institute for Health and Care Research (NIHR) (UK)

Who is the main contact?
Jade.harris@nca.nhs.uk

Contact information

Type(s)
Scientific

Contact name
Dr Fiona Bray

Contact details
Deputy Research & Innovation Manager
Northern Care Alliance NHS Foundation Trust
Summerfield House
544 Eccles New Road
Salford
United Kingdom
M5 5AP
None provided
fiona.bray@nca.nhs.uk

Type(s)
Scientific

Contact name
Prof Mats Tullberg

Contact details
University of Gothenburg
Sahlgrenska University Hospital
Bla straket 7
Goteborg
Sweden
SE 41345
+46768672618
mats.tullberg@neuro.gu.se

Type(s)
Scientific

Contact name
Prof Neil Reeves

ORCID ID
https://orcid.org/0000-0001-9213-4580

Contact details
Faculty Head of Research and Knowledge Exchange (RKE)
Manchester Metropolitan University
John Dalton Building
Oxford Road
Manchester
United Kingdom
M1 5GD
+44 (0)161-247-5429
n.d.reeves1@lancaster.ac.uk

Type(s)
Scientific

Contact name
Dr Richard Mills

ORCID ID
https://orcid.org/0000-0002-3249-7539

Contact details
Senior Lecturer in Biomechanics | Programme Lead, Sport & Exercise Sciences
Manchester Metropolitan University
All Saints Building, Room 407
Oxford Road
Manchester
United Kingdom
M15 6BH
+44 (0)161 247 5470
richard.mills@mmu.ac.uk

Type(s)
Scientific

Contact name
Dr Cliff Chen

Contact details
Clinical neuropsychologist
Northern Care Alliance NHS Foundation Trust
Salford Royal Hospital
Clinical Sciences Building

Stott Lane
Manchester
United Kingdom
M6 8HD
+44(0)1612062004
cliff.chen1@nhs.net

Type(s)
Scientific

Contact name
Dr Tobias Langheinrich

ORCID ID
https://orcid.org/0000-0002-4714-8657

Contact details
Salford Royal NHS Foundation Trust
Salford Royal
Stott Lane
Manchester
United Kingdom
M6 8HD
None provided
tobias.langheinrich@nca.nhs.uk

Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
302102

Protocol serial number
CPMS 53894, IRAS 302102

Study information

Scientific Title
Utility of three-dimensional gait analysis in reference to clinical assessments to detect significant change after a cerebrospinal fluid tap test in patients investigated for idiopathic normal pressure hydrocephalus

Study objectives
It is hypothesised that:
1. Those with idiopathic normal pressure hydrocephalus (iNPH) will exhibit decreased gait velocity (slower walking), increased step width variability, unsteadiness (increased centre of mass trajectories), reduced joint ranges of motion, and poorer balance test scores when compared to age-matched controls;

2. Gait outcome variables will improve following the tap test; and
3. In view of the low negative predictive value but high specificity of the TT gait analysis will be more sensitive than clinical assessments at demonstrating change.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 11/10/2022 East Midlands - Leicester Central Research Ethics Committee (Equinox House, City Link, Nottingham, NG2 4LA; +44 (0)207 104 8066, (0)207 104 8199; leicestercentral.rec@hra.nhs.uk), ref: 22/EM/0213

Study design
Observational cross-sectional design followed by an interventional prospective design

Primary study design
Interventional

Study type(s)
Treatment

Health condition(s) or problem(s) studied
Idiopathic normal pressure hydrocephalus

Interventions
The clinical aim of the study is to improve detection rates of pwN likely to benefit from ventriculoperitoneal (VP) shunt. The objective is to optimise mobility assessments before and after TT that are used to detect improvement, which, if present, confers pwN a high likelihood of benefitting from permanent treatment with VP shunt. The scientific aim of the study is the introduction of highly sophisticated laboratory techniques to objectively quantify walking and balance (3D) which has not been used in iNPH before. It has 2 parts. In the cross-sectional, controlled, observational part 3D of the clinical assessments (CA) of pwN will be compared to that of HC. In the prospective, interventional part 3D of the CA will be compared in pwN before and after TT. The cross-sectional part has hypothesis-generating and hypothesis-driven components. The hypothesis-generating component seeks to define typical 3D characteristics of pwN by comparing it to HC, the hypothesis-driven component posits that 3D will be able to confidently separate pwN from HC. The prospective part applies the findings of the hypothesis-generating component by comparing the 3D and CA of pwN before and after TT. Another hypothesis-driven component posits that 3D will be able to better detect change between the two assessments than CA.
Participant groups have been carefully defined based on specific inclusion/exclusion criteria. Consecutive people with iNPH will be recruited from the regional specialist NPH clinic at The Manchester Centre for Clinical Neurosciences at Salford Royal Hospital, Northern Care Alliance NHS Foundation Trust, UK. As part of their clinical routine, they are assessed by a senior neurologist with a specialist interest in cognitive neurodegenerative disease. If iNPH is a diagnostic possibility, they are admitted for TT. Two patients per week are tested on average. During that admission, they are assessed by a senior neuropsychologist with a specialist interest in differential diagnostic assessments of patients with dementing disorders. They undergo advanced MRI scanning of the brain. Clinical examination of gait and balance before and after TT is carried out and video-recorded by a neurophysiotherapist.
Cerebrospinal fluid obtained during TT is analysed for neurodegeneration markers. A consensus

diagnosis is reached in a subsequent multidisciplinary team meeting during which all data are reviewed.
Both groups will undergo the same laboratory-based testing protocols to assess their gait and balance. Participants in the control group will be invited to attend a single testing visit at the gait laboratory at Manchester Metropolitan University. Participants with iNPH will be invited for a second test session the day after the tap test to assess the effects of the procedure on gait (change score on outcome measures).
We will use a 16-camera 3-dimensional motion analysis system to accurately track the movement of markers positioned on specific anatomical landmarks of each participant's body while walking. Force plates embedded in a bespoke floor-mounted walkway will provide accurate measurements of ground reaction forces under the feet as the participant walks across them. These measures will provide a detailed understanding of the movement of the limbs and the whole body, and the rotational forces developed around all lower limb joints. We also have the ability to record muscle activity through surface electromyography, which provides insight into when, and by how much, muscles are being utilized to perform a task. We will examine gait with a range of support conditions (e.g. with the natural use of preferred walking aid if required; with assistance from partner/carer/researcher; with use of a standardised minimal walking aid such as a cane/stick; and without any assistance if possible) to allow appropriate comparison against controls and pre-post treatment. The static balance will be examined through quiet stance (e.g. 30 seconds standing on force plates; centre of pressure and centre of mass trajectories and their time derivatives to be analysed), and dynamic balance examined during gait. Continuous data sets will be generated and used to quantify different aspects of gait and balance function.
Gait variables of interest: The research team have extensive experience in investigating clinical movement impairment across a range of other clinical conditions including diabetes, stroke and Parkinson's. While measuring the full range of detailed gait variables, based on our experience and evidence from the literature, we hypothesise analysis may focus on some key variables. These include a measure of 'dynamic balance' that evaluates the movement (sway) in the body's centre of mass relative to the centre of pressure under the feet, shown to be a sensitive measure of gait impairment in diabetic neuropathy (Brown et al., 2015). Other variables of focus based on previous research include step length, gait velocity and temporal-spatial measures of gait variability. Based on the team's clinical experience of iNPH gait and from our recent Patient and Public Involvement (PPI) sessions in preparation for this project, patients tell us they sometimes experience the feeling of their feet "sticking to the floor" and in this respect, we hypothesize that the temporal-spatial gait variables (reflecting timing and distance of gait) events might be particularly pertinent.
Remote physical activity monitoring devices (Fitbits) will be supplied to all participants (patients and controls) when they attend for their first visit to the gait laboratory. Patients start monitoring their activity levels 7 days prior to their lumbar puncture until 7 days post-lumbar puncture; controls monitor from 7 days before until 7 days after they have attended the gait lab. Patients and controls will be asked to record the amount of daily activity during this time period.
Psychological factors will be monitored in patients (part of the clinical routine) and controls using the Hospital Anxiety and Depression Scale (when they attend the gait laboratory). Quality of life will be assessed with the EQ-5D-5L patient version (patients -part of the clinical routine- and controls when they attend the gait laboratory) and EQ-5D-5L proxy versions (patients only, part of the clinical routine) and carer burden will be assessed with the Burden Scale for Family Caregivers (patients only, part of the clinical routine). These secondary assessments will provide insight into clinically relevant outcomes of everyday activity in the period immediately following the tap test and may be relevant to the participant's performance. We will also evaluate participants' experience and expectations of their gait and balance performance pre and post-tap test when measured clinically and with gait analysis assessing for concordance and participants' reaction to the results using a semi-quantitative questionnaire (part of the clinical routine). Patients are followed closely after the TT as part of their clinical routine to discuss the

results and plan further management.
Researcher bias is not an issue for the 3D. Healthcare workers carrying out and analysing the CA are working according to standardised clinical protocols and for ecological validity, researcher bias is not reduced any further (for logistical reasons not possible to guarantee that raters are blinded for example).
Key gait and balance variables that can be used to characterize iNPH will be determined through the use of logistic (discriminant) regression analyses between patients and healthy controls. Given the sample size of this initial study, variables will be considered unifactorially. A similar approach will be used to estimate the Receiver Operating Characteristic (ROC) curve for these variables as screening tools for shunt surgery. Standardised effect sizes for the key gait and balance variables will be compared informally with those derived for currently routine clinical measures by repeating the above analyses.
This study will obtain data necessary to estimate the sample size for a large-scale, pivotal randomized controlled trial. We will obtain 1) an estimate of the variability of the change score on primary outcome measures; 2) a correlation between baseline and follow-up scores (r-value); and 3) the smallest clinically meaningful between-group effect for the primary outcomes.

Intervention Type
Other

Primary outcome(s)
All measures are assessed ~1 week apart (~7 days pre- and within 72hrs post-lumbar puncture for pwN); controls test only once
Gait lab assessments will include:
1. 10-minute walk test
2. Timed up and go test
3. 360-degree turn test
4. Balance tests (quiet stance (60 seconds)
5. Single leg stance (seconds able)
6. Romberg test (seconds able to stand with eyes closed)

Variables to be included in analyses from above are those found in standard 3d gait and balance assessments:
Kinetic variables of interest will include forces (mediolateral, anteroposterior, and vertical ground reaction forces; joint forces, moments and powers) and centre of pressure
Kinematic variables of interest will include joint angles, angular velocities, whole body centre of mass displacement/velocity/acceleration, temporospatial measures (walking distance/time /speed; stride length, width, cadence)

Key secondary outcome(s))
Psychological factors will be monitored in patients (part of the clinical routine) and controls before, 1 h and 24 hours post lumbar puncture, and each time before and after mobility assessments:
1. Anxiety and depression symptoms measured using the Hospital Anxiety and Depression Scale when they attend the gait laboratory
2. Quality of life measured using:
2.1. Patient version of the EQ-5D-5L in patients as part of the clinical routine and in controls when they attend the gait laboratory
2.2. Proxy version of the EQ-5D-5L in patients only as part of the clinical routine
3. Carer burden measured using the Burden Scale for Family Caregivers in patients only as part of the clinical routine

Step counts, distance walked, heart rate (resting; variability), skin temp variation, breathing rate, sleep tracking and calories expended measured using Fitbit data in the 3 days pre-LP and 1 week post LP

Completion date
26/03/2025

Eligibility

Key inclusion criteria
1. Consenting males and females diagnosed with iNPH according to the international guidelines for diagnosing iNPH. Patients younger than age 60 may be included on a case-by-case basis.
2. Should be able to walk unaided for at least 20 steps at a time; walking aids will be permitted to reflect the reality of this condition for many patients.
3. Consenting healthy volunteers, of similar age and sex distribution, without iNPH. Chronic stable health conditions and chronic stable medications (e.g. hypertension on long-term antihypertensive medication) with no substantive impact on performance and participation in this study as judged by the investigators are permitted.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Sex
All

Total final enrolment
44

Key exclusion criteria
1. Other confirmed medical or surgical conditions better explaining symptoms than iNPH (patients) or with substantive impact (eg Parkinson’s, osteoarthritis) as judged by the investigators (patients and control)
2. Secondary or obstructive hydrocephalus; previous surgical procedures for hydrocephalus (patients)
3. Amputation of lower limb/appendages
4. Musculoskeletal injury/recent lower-limb surgeries affecting gait or other musculoskeletal ailments affecting gait and balance performance as judged by the investigators
5. Participants on specific medications (eg centrally acting) better explaining symptoms than iNPH (patients) or with substantive impact as judged by the investigators (patients and control)
6. Unable to carry out all study procedures
7. Unable to comprehend informed consent

Date of first enrolment
01/01/2023

Date of final enrolment
30/09/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Northern Care Alliance NHS Foundation Trust
Salford Royal
Stott Lane
Salford
United Kingdom
M6 8HD

Study participating centre
Manchester Metropolitan University
Department of Sport and Exercise Sciences
Oxford Road
Manchester
United Kingdom
M15 6BH

Sponsor information

Organisation
Salford Royal NHS Foundation Trust

ROR
https://ror.org/019j78370

Funder(s)

Funder type
Charity

Funder Name

Hydrocephalus Association

Alternative Name(s)
HYDROCEPHALUS ASSN, Hydrocephalus Assoc., HA

Funding Body Type
Government organisation

Funding Body Subtype
Associations and societies (private and public)

Location
United States of America

Funder Name
National Institute for Health and Care 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

Individual participant data (IPD) sharing plan
The datasets generated during and/or analysed during the current study will be stored in a publicly available repository

IPD sharing plan summary
Stored in publicly available repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No
Protocol file	version 2	08/09/2022	19/01/2023	No	No