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A novel test (RT-QuIC) to differentiate between two types of REM Behavioural Disorder (RBD) - pRBD (which is a potential indicator of future development of Parkinson's Disease) and iRBD (which is not thought to be)

Submission date
07/01/2020

Recruitment status
Stopped

Registration date
06/02/2020

Overall study status
Stopped

Last Edited
17/10/2022

Condition category
Mental and Behavioural Disorders

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

Plain English summary of protocol

Background and study aims
Rapid Eye Movement Sleep Behaviour Disorder (RBD) is a sleep disorder in which people act out their dreams. Previous studies have found a high conversion rate from RBD to subsequent neurodegenerative disease, with the majority of patients developing one of the α-synucleinopathies (Parkinson's disease, multiple system atrophy, Lewy body dementia). As not all RBD patients go on to develop a neurodegenerative disease (40 - 80.8% in 16 to 25 years of follow-up), and RBD only presents as a comorbidity in a percentage of patients with α-synucleinopathies (30% of Parkinson's disease patients have RBD), it is important to identify factors which robustly provide prognostic data on the clinical course of RBD. The aim of this study is to develop and validate a test for the detection of pathological protein (α-syn RT-QuIC) that can be used to differentiate between cases of RBD that subsequently progress to a neurodegenerative disorder such as Parkinson's disease and those that do not.

Who can participate?
Patients aged over 18 with a diagnosis of RBD

What does the study involve?
All data is collected in one 90-minute appointment, which takes place at the Wellcome Trust Clinical Research Facility (WTCRF) at either Royal Infirmary of Edinburgh or Western General Hospital Edinburgh. The appointment involves a clinical examination and interview, blood sampling and cerebrospinal fluid (CSF) sampling via lumbar puncture. Participants are interviewed with regards to their lifestyle, medical history and comorbidities. Participants are asked to fill out sleep diaries and questionnaires relating to their sleep. All patients are examined clinically regarding motor function and anosmia. Markers of autonomic dysfunction

are also tested for using simple techniques such as an orthostatic standing test. Any individuals who have already developed PD are interviewed with regards to their neurodegenerative presentation, e.g. response to drug treatment.

What are the possible benefits and risks of participating?
Whilst there is no direct benefit to the individual participant, their participation in the study will help to develop a test which may benefit many other patients with RBD in the future. Time burden to the patient is minimal, with only a single 90-minute study visit required. Blood sampling is generally well-tolerated. Minor discomfort and bruising may occur at the needle site but should self-resolve quickly. Some individuals may feel dizzy or faint, and can lie down during the procedure. A lumbar puncture is generally a safe procedure and serious side effects are uncommon. The most common side effects include headaches, which can last for up to a week and can be relieved using over-the-counter painkillers, and swelling and lower back pain where the needle was inserted, which should get better after a few days and is normally nothing to worry about. The questionnaires used contain personal questions which some individuals may find intrusive or uncomfortable to answer, though all information is required purely to make a complete clinical assessment.

Where is the study run from?
University of Edinburgh/NHS Lothian Royal Infirmary (UK)

When is the study starting and how long is it expected to run for?
January 2020 to September 2023 (updated 21/04/2020, previously: June 2023)

Who is funding the study?
Weston Brain Institute (UK)

Who is the main contact?
Dr Renata Riha
rriha1@staffmail.ed.ac.uk

Contact information

Type(s)
Public

Contact name
Mr Steven Williams

Contact details
Chancellors Building
Room 305
49 Little France Crescent
Edinburgh
United Kingdom
EH16 4SB
+44 (0)7903029892
picklish@hotmail.com

Type(s)
Scientific

Contact name
Dr Renata Riha

Contact details
Chancellors Building
Room 305
49 Little France Crescent
Edinburgh
United Kingdom
EH16 4SB
+44 (0)131 242 3882
rriha1@staffmail.ed.ac.uk

Additional identifiers

Protocol serial number
Funder's Reference Number - 16021036.1

Study information

Scientific Title
Establishing alpha-synuclein Real Time - Quaking Induced Conversion (RT-QuIC) assay as a diagnostic technique in REM sleep behaviour disorder (RBD)

Acronym
RTQUIC&RBD

Study objectives
The researchers hypothesise that a real-time quaking induced conversion assay for the detection of pathological alpha-synuclein (α -syn RTQuIC) can be used to differentiate between cases of idiopathic REM-sleep behaviour disorder (RBD) and RBD that is symptomatic of prodromal α-synucleinopathies. With a patient sample size of n=125, this multicentre study will be the largest analysis of CSF α-synuclein in RBD patients to date. In line with The National CJD Research & Surveillance Unit (NCJDRSU)'s recent inclusion of a positive RT-QuIC for pathological prion protein in the diagnostic criteria for Creutzfeldt-Jakob Disease (CJD), the researchers aim to deploy this novel method to establish it as an accurate research and diagnostic resource in the assessment and prognosis of RBD. This research is transformative and has the potential to change practice. Currently, there is no simple method with high sensitivity and specificity available which can identify patients who will go on to develop an α - synucleinopathy. Clinical assessment of a panel of markers (e.g. Postuma et al. 2015) are time-consuming and impractical in normal clinical settings, with the majority of patients presenting to sleep physicians, geriatricians, and non-specialised neurology clinics, both publicly and privately. This has a major impact on counselling strategies for RBD patients, appropriate follow-up, trials of novel neuroprotective agents in alpha-synucleinopathies before full-blown phenotype is manifest and enhancing understanding of pathways involved in RBD out-with the dopaminergic system. RBD is a common, sometimes fatal disease (through injury to self/others) and treatments are indiscriminate regarding aetiology with limited evidence-base. A simple test using CSF (analogous to measuring CSF-orexin levels to diagnose narcolepsy+cataplexy) with high sensitivity and specificity is ideal. Thus, the researchers believe that the central thesis of their

work will not only inform subsequent behavioural, genetic and neuroimaging characterisation of their established RBD cohort, but will also translate the α-syn RT-QuIC concept into evidence-based and effective clinical practice.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 23/03/2020, South East Scotland Research Ethics Committee 1 (NHS Lothian, Waverley Gate, 2 - 4 Waterloo Place, Edinburgh, EH1 3EG, UK; +44 (0)131 465 5473; Sandra.Wyllie@nhslothian.scot.nhs.uk), ref: DL/20/ES/0032

Primary study design
Observational

Study design
Cross-sectional multicentre study

Study type(s)
Screening

Health condition(s) or problem(s) studied
REM behavioural disorder and Parkinson's disease

Interventions
This is a cross-sectional, multi-centre study using the CSF of patients with RBD which may or may not develop into a neurodegenerative disease, as well as patients with RBD who have already developed an α-synucleinopathy. The proposed study length is 3 years (36 months). Participant involvement will be approximately 30 months from receipt of invitation letter to dissemination of results. The researchers envisage ongoing follow-up of this group of patients into the future to assess for development of a α-synucleinopathy to further confirm the utility of this technique in day-to-day clinical practice.

Participants will be recruited from sleep clinics and existing RBD patient cohort databases under the care of the Department of Sleep Medicine, Royal Infirmary of Edinburgh and the Behavioural Sleep Medicine Department, Ninewells Hospital, Dundee. Together, these departments have an unselected RBD cohort of approximately 250 patients, from which the researchers aim for a sample size of 125 patients.

Participants who consent to participate will be invited to a single, 90 minute, appointment at the clinical research facility (CRF) at either the Royal Infirmary of Edinburgh or Western General Hospital, Edinburgh. Participants will be interviewed with regards to their lifestyle and medical history. They will be asked to fill out sleep diaries and questionnaires relating to their sleep and will be examined clinically for possible symptoms of PD and, in individuals who have already been diagnosed with PD, their response to drug treatment. A 9 ml blood sample will be collected as part of clinical evaluation. During the lumbar puncture, 1.5 ml of CSF will be collected. The samples will be stored at -80C prior to analysis.

Participants will be observed for the duration of the trial (36 months), and further funding sought to continue long-term follow-up of RBD cohort participants.

Intervention Type
Other

Primary outcome(s)
Positive/negative (binary) result from the α-syn RT-QuIC assay. A positive output confirms the presence of pathological α-synuclein within the CSF. Measured using lumbar puncture to obtain CSF at a single trial visit.

Key secondary outcome(s)
All measures will take place at the patient's only trial visit:
1. Screening for co-morbidities using a medical history questionnaire
2. Screening for REM Behavioural disorder with the RBDQ-HK questionnaire
3. Excessive daytime sleepiness assessed using the Epworth Sleepiness Scale
4. Sleep pattern assessed using a sleep diary
5. Stressful events that might cause illnesses assessed using the Holmes and Rahe stress scale
6. Orthostatic hypotension assessed using the Orthostatic Standing Test
7. Clinical rating scale for Parkinson's disease using the MDS-UPDRS questionnaire
8. Venepuncture to obtain 9 ml of blood for future genetic testing in follow-up study

Completion date
01/09/2023

Reason abandoned (if study stopped)
Lack of staff/facilities/resources

Eligibility

Key inclusion criteria
1. Diagnosis of RBD based on International Classification of Sleep Disorders 3rd Edition (ICSD-3) criteria
2. Aged 18 years or over
3. Willing and able to give written informed consent and comply with protocol

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 Years

Sex
All

Key exclusion criteria

1. RBD secondary to medication or withdrawal state
2. <18 years old
3. Unwilling or unable to give written informed consent or comply with protocol
4. Contraindication to lumbar puncture procedure (e.g. patients taking Warfarin)

Date of first enrolment
01/10/2021

Date of final enrolment
01/12/2022

Locations

Countries of recruitment
United Kingdom

Scotland

Study participating centre
NHS Lothian
Waverley Gate
2-4 Waterloo Place
Edinburgh
United Kingdom
EH1 3EG

Study participating centre
NHS Tayside
Ninewells Hosptial and Medical School
James Arrott Drive
Dundee
United Kingdom
DD1 9SY

Study participating centre
The University of Edinburgh
The National Creutzfeldt-Jakob Disease Research and Surveillance Unit
Brian Matthews Building
Western General Hospital
Edinburgh
United Kingdom
EH4 2XU

Sponsor information

Organisation
ACCORD

Funder(s)

Funder type
Research organisation

Funder Name
Weston Brain Institute

Results and Publications

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

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			28/06/2023	No	No