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Carbon spectroscopy MRI: a non-invasive tool to detect late-onset Pompe disease (LOPD)

Submission date
15/06/2022

Recruitment status
No longer recruiting

Registration date
07/07/2022

Overall study status
Completed

Last Edited
05/04/2024

Condition category
Nutritional, Metabolic, Endocrine

[_] 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
Pompe disease, also known as Glycogen Storage Disease type II, is a genetic disorder produced by mutations in the GAA gene resulting in an absence or low levels of the enzyme alpha-glucosidase which is needed to convert glycogen to glucose in cells. This leads to a build-up of glycogen in the cells of several tissues, particularly cardiac, skeletal, and smooth muscle cells. Most late-onset Pompe disease (LOPD) patients notice their first symptoms during the third or fourth decade of life. Patients slowly develop progressive muscle weakness leading to a variable degree of motor disability. Most patients need canes for walking during the fourth decade of life and a wheelchair in the fifth or sixth decade of life. Respiratory symptoms and respiratory failure requiring non-invasive ventilation are common. Adult patients can have an increased risk of premature death due to respiratory problems.
Enzyme replacement therapy (ERT) improves muscle weakness and reduces the need for supporting ventilation in patients treated. Guidelines recommend starting the treatment only in symptomatic patients with muscle weakness involving skeletal or respiratory muscles. However, compelling evidence suggests earlier treatment in LOPD can result in better outcomes. The build-up of glycogen inside muscle fibres leads to muscle fibre loss and the replacement of muscle with fatty tissue. Fat replacement is irreversible and can lead to permanent weakness and disability. Therefore, an effort to avoid or slow the process of muscle fibre loss and fatty tissue expansion is essential. Repeated biopsies (tissue samples) of LOPD patients showed a reduction in glycogen in muscles with ERT. Therefore, in theory, earlier treatment of LOPD patients, whose muscles are not replaced by fat yet but contain high levels of glycogen, should delay muscle worsening and avoid permanent motor and respiratory disability. However, we do not currently have a non-invasive test capable of identifying and/or calculating muscle glycogen. The aim of this study is to use an MRI (Magnetic Resonance Imaging) sequence known as 13C-spectroscopy to identify glycogen in the skeletal muscles of patients with LOPD who are still pre-symptomatic or who have minor symptoms. 13C-spectroscopy has previously been shown to identify glycogen in different organs of the body, including skeletal muscle. One study that included 11 LOPD patients showed the average levels of glycogen in muscles was higher than controls for seven out of the 11 patients. However, it was unclear if there were differences in the amount of glycogen over time.
This study aims to use a second MRI sequence known as T2-weighted imaging that provides information about the composition of the skeletal muscles. Glycogen accumulation in muscles

may be associated with a change in the T2 relaxation properties of water in muscle. We will assess whether muscle T2 is different in LOPD patients compared to healthy controls. Additionally, the researchers will use a series of muscle function tests to confirm that patients do not have any sign of muscle damage, and are pre-symptomatic or mildly symptomatic. It is thought that both 13C-spectroscopy and T2 imaging can be useful to identify the accumulation of glycogen in the muscle tissue of these patients and can be used to monitor changes in the concentration of glycogen in the tissue over time.

Who can participate?
Patients with genetically confirmed pre-symptomatic or early symptomatic late-onset Pompe disease (i.e., started showing symptoms after the age of 3 years) aged 12 years and older; and 10 healthy volunteers who are age- and sex-matched with the Pompe patients.

What does the study involve?
Patients with Pompe disease will attend two visits, at the start of the study and after 12 months. Healthy volunteers will attend once only. During the first visit researchers will perform a clinical assessment, a series of muscle function tests, collect patient-reported outcome measures, obtain blood samples, and perform an MRI scan. Muscle function tests will include muscle strength and muscle performance. At 12 months only the Pompe patients will attend the second visit where all the first visit measures will be repeated.

What are the possible benefits and risks of participating?
There are no potential risks as there are no invasive procedures involved in this study. MRI scanning is a safe repeatable medical imaging method that does not involve the use of ionising radiation. Blood collection does not pose a significant risk nor do the muscle function tests. Participants are not expected to directly benefit from this study. All travel and meal expenses will be reimbursed for the patient and one accompanying person.

Where is the study run from?
Newcastle upon Tyne Hospitals NHS Foundation Trust (UK)

When is the study starting and how long is it expected to run for?
January 2022 to December 2025

Who is funding the study?
Sanofi (France)

Who is the main contact?
Prof. Jordi Diaz-Manera, jordi.diaz-manera@newcastle.ac.uk

Contact information

Type(s)
Principal investigator

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
305745

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
NU-003493, IRAS 305745, CPMS 51417

Study information

Scientific Title
Muscle MRI as a tool to detect glycogen in the skeletal muscles of patients with adult-onset Pompe patients

Acronym
MRI in Pompe

Study objectives
It is hypothesized that 13C spectroscopy can quantify skeletal muscle glycogen content in patients with Pompe disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 24/01/2022, Yorkshire & The Humber - Leeds West Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 972 2504, +44 (0)207 104 8134; leedswest.rec@hra.nhs.uk), ref: 21/YH/0297

Study design
Single-centre prospective observational cohort study

Primary study design
Observational

Study type(s)
Diagnostic

Health condition(s) or problem(s) studied
Pompe disease in adult-onset patients

Interventions
This study will consist of clinical assessments, collection of blood samples, a series of muscle function tests and collection of patient-reported outcome measures. The participants with Pompe disease will attend two visits over 1 year (baseline and year 1).

13C-magnetic resonance spectroscopy offers a non-invasive measurement by direct MRI-based detection of a unique signal from natural abundance 13C in glycogen. T2 sequence of muscle water will be obtained from the same MRI as well.

Intervention Type
Other

Primary outcome(s)
Glycogen measured using 13C spectroscopy for patients and controls at baseline and at the 12-month visit for patients only

Key secondary outcome(s))
1. Water accumulation measured using water T2 sequence at baseline for patients and controls and at the 12-month visit for patients only
2. Muscle function measured using muscle strength and performance tests at baseline for patients and controls and at 12 months for patients only

Completion date
31/12/2025

Eligibility

Key inclusion criteria
Current participant inclusion criteria as of 05/04/2024:
Patients:
1. Diagnosis of Pompe disease based on recommendations recently proposed by the European Pompe Consortium: reduced enzymatic activity in leukocytes, fibroblasts or skeletal muscle and /or by the presence of two mutations in the GAA gene following the diagnostic
2. Aged 12 years and older
3. No contraindications to MRI
4. No symptoms of muscle weakness or mild symptoms
5. Willingness to complete all muscle function tests at baseline and year 1 visit

Healthy controls:
1. Male and female age-matched with the patients (12 years and older)
2. No contraindications to MRI
3. Willingness to complete all study assessments

Previous participant inclusion criteria:
Patients:
1. Diagnosis of Pompe disease based on recommendations recently proposed by the European Pompe Consortium: reduced enzymatic activity in leukocytes, fibroblasts or skeletal muscle and /or by the presence of two mutations in the GAA gene following the diagnostic
2. Aged 12 years and older
3. No contraindications to MRI
4. No symptoms of muscle weakness or mild symptoms. Patients should score higher than 30 points on the RPact scale
5. Willingness to complete all muscle function tests at baseline and year 1 visit

Healthy controls:
1. Male and female age-matched with the patients (12 years and older)
2. No contraindications to MRI
3. Willingness to complete all study assessments

Participant type(s)
Mixed

Healthy volunteers allowed
No

Age group
Mixed

Lower age limit
12 years

Sex
All

Key exclusion criteria
1. Contraindications for MRI such as having a metallic prosthesis, pacemaker or any other device that makes the completion of an MRI impossible
2. Not willing to complete all muscle function tests both at baseline and year 1 (just patients)
3. Having claustrophobia or other condition that could limit the capacity of the patient for being located inside the MRI
4. Inability to lie supine for less than 45 min
5. Pregnancy (for female participants of childbearing age only)
6. Not being able to understand and speak English (added 17/01/2023: unless accompanied by a translator)
7. Study team decision that it is not in the best interests of the patient to participate in the study

Date of first enrolment
01/06/2022

Date of final enrolment
31/12/2024

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
The Newcastle upon Tyne Hospitals NHS Foundation Trust
Freeman Hospital
Freeman Road
High Heaton
Newcastle upon Tyne
United Kingdom
NE7 7DN

Study participating centre
John Walton Muscular Dystrophy Research Centre
Institute of Genetic Medicine
Newcastle University
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NE1 3BZ

Study participating centre
Newcastle Magnetic Resonance Centre
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Study participating centre
NIHR Newcastle Clinical Research Facility
Level 6 Leazes Wing
Royal Victoria Infirmary
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Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Industry

Funder Name
Sanofi

Alternative Name(s)
sanofi-aventis, Sanofi US, Sanofi-Aventis U.S. LLC, Sanofi U.S.

Funding Body Type
Government organisation

Funding Body Subtype
For-profit companies (industry)

Location
United States of America

Results and Publications

Individual participant data (IPD) sharing plan
We will not be depositing raw data in publicly available repositories. Larger follow on studies have the participant-level data submitted to public repositories. After the study has ended the site files will be stored securely in the locked filing cabinet. These will be archived following the Newcastle Hospitals NHS Foundation Trust policies for longer-term storage.

IPD sharing plan summary
Not expected to be made available

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
HRA research summary			26/07/2023	No	No
Participant information sheet	PIS for adult healthy controls version 1.1	14/01/2022	23/06/2022	No	Yes
Participant information sheet	PIS for adult patients version 1.1	14/01/2022	23/06/2022	No	Yes
Participant information sheet	PIS for healthy controls aged 12+ version 1.1	14/01/2022	23/06/2022	No	Yes
Participant information sheet	PIS for parents of healthy controls version 1.1	14/01/2022	23/06/2022	No	Yes
Participant information sheet	PIS for parents of patients version 1.1	14/01/2022	23/06/2022	No	Yes
Participant information sheet	PIS for patients aged 12+ version 1.1	14/01/2022	23/06/2022	No	Yes
Participant information sheet	version 2.0	04/04/2023	05/04/2024	No	Yes

Participant information sheet	version 2.0	04/04/2023	05/04/2024	No	Yes
Participant information sheet	version 2.0	04/04/2023	05/04/2024	No	Yes
Participant information sheet	version 2.0	04/04/2023	05/04/2024	No	Yes
Participant information sheet	version 2.0	04/04/2023	05/04/2024	No	Yes
Participant information sheet	version 2.0	04/04/2023	05/04/2024	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes
Protocol file	version 1.0	20/10/2021	23/06/2022	No	No
Protocol file	version 2.0	04/04/2023	05/04/2024	No	No