ISRCTN15622536 https://doi.org/10.1186/ISRCTN15622536

Cardiac arrhythmias in Duchenne & Becker muscular dystrophy (BDMD)

Submission date
09/02/2021

Recruitment status
No longer recruiting

Registration date
29/03/2021

Overall study status
Completed

Last Edited
04/04/2024

Condition category
Nervous System Diseases

[ ] Prospectively registered
[ ] Protocol
[ ] Statistical analysis plan
[X] Results
[ ] Individual participant data

Plain English summary of protocol

Background and study aims
This study aims to define whether minimally symptomatic disturbances of the heart rhythm occur in patients with severely weakened heart pumping function (cardiomyopathy), as part of the generalized muscle wasting conditions Duchenne muscular dystrophy (DMD) or Becker muscular dystrophy (BMD). Sudden deaths do occur in these patients but could be due to excessively fast or profoundly slow heart electrical activity or to other non-rhythm causes.

Hearts that are severely weakened from any cause become electrically unstable. This can cause very fast or very slow heart rhythms resulting in loss of heart function in pumping blood around the body. For example, sustained, very fast rhythms will present as cardiac arrest, and is the cause of most sudden deaths in patients following a heart attack. However, in dilated forms of cardiomyopathy, a similar loss of heart function can equally be caused by very slow heart rhythms. Additionally, in patients with advanced heart failure, due to stagnant blood flow in the veins can result in a major blood clot in the blood vessels of the lungs. Each of these outcomes could present similarly, a previously stable patient would become acutely unwell, lose consciousness and die within minutes. Sudden death does occur in patients with cardiac dystrophinopathy but the mechanism by which this occurs is currently unclear. This means that it is currently unknown whether, and to what extent, sudden deaths could be prevented by pacemakers or implantable defibrillator therapy.

Defining and detecting warning rhythms would for the first time allow preventative treatments to be designed and tested in patients with BMD or DMD (BDMD). Previous studies in patients after heart attacks or with comparable degrees of heart-pumping weakness due to non-BDMD forms of cardiomyopathy have shown that the occurrence of short-duration periods of unusual heart rhythms without symptoms (warning rhythms) are already known to correlate with the occurrence of lethal rhythms.

The study aims to find out how often fast or slow heart rhythms without symptoms occur in patients with BDMD and advanced reduced heart pumping function using implanted devices to record the heart rhythm. The study will also measure the size, shape, and distribution of scarring of the heart in patients or female gene-carriers, and will compare scarring between patients with BDMD and patients following a heart attack or other disease of the heart muscle who have

similar heart function. The findings will help determine whether sudden deaths in patients with BDMD could be prevented by pacemaker/implantable defibrillator therapy.

Who can participate?
Adults with Duchenne or Becker muscular dystrophy (BDMD) or female BDMD-mutation carriers with similar severity of heart dysfunction.

What does the study involve?
All participants will be required to have an ECG-loop recorder implanted beneath the skin to the left side of the chest under sterile conditions and using local anaesthesia in a procedure taking about 30 min. This will typically be within two months of study entry. There are no direct connections between the device and the heart, unlike a pacemaker, these devices just record ECGs but do not provide any form of treatment.

Ideally, all patients will undergo MR-imaging of the heart on one occasion. This form of heart scanning takes about 45-60 min to complete and involves the administration of Gadolinium into an arm vein. This is to allow visualisation of scars in heart muscle. However, patients unable to undergo cMRI safely, or who are unable to tolerate the scanning process, can still be recruited to the ECG-rhythm surveillance part of the study.

The implanted loop recorder has battery life for about three years and will be programmed to detect pre-defined episodes of abnormally fast or slow heart rhythms automatically, regardless of symptoms. Participants can also record an ECG at the time of symptoms using an ‘activator’ device. Loop-recorders communicate with the hospital automatically by means of a remote monitoring system uniquely linked to each device. This allows the device to upload what it has recorded remotely and automatically via a dedicated transmitter connected to the patient’s home phone. This means that patients do not have to come to the hospital to download data and the device provides comprehensive rhythm surveillance 24 h/day. Each patient exits the study six months after the start of heart rhythm surveillance, six months after the loop-recorder implant.

Participants will be required to complete quality of life questionnaires at study entry and at six months after device implant.

Patients will have the option of having their device explanted either as they exit the study after six months or after battery depletion after about three years. Rhythm surveillance will continue to be provided through normal clinical arrangements for those who opt to keep their device beyond the six months term of this research. The loop-recorder is removed in a procedure taking about 30 min, performed under sterile conditions, and requiring local anaesthesia as the implant procedure.

What are the possible benefits and risks of participating?
There are no direct benefits to patients taking part in this research. However, some patients may benefit from knowing that their heart rhythm is being monitored continuously and that any abnormalities are being 'seen', interpreted and, when appropriate, acted upon promptly.

The only risk envisaged is the remote possibility of local subcutaneous infection at the site where the loop-recorder is implanted. As there are no connections between loop-recorders and the heart, this would be treated by device removal and a short course of antibiotic therapy. There would be minimal risk of wider sepsis. All implants will be performed by trained operators on a day case basis in a suitably aseptic environment.

Cardiac MR-imaging takes about 60 min and requires access to a vein. Some patients have very limited veinaccess due to limb contractures. Additionally, it is more difficult for adult patients with BDMD to be placed in the scanner and for them to be comfortable during imaging than for more able-bodied patients. Patients with various forms of muscular dystrophy regularly undergo and tolerate cardiac MR-imaging as part of their clinical management and staff in the Radiology Department are experienced in optimizing patient positioning and limiting their time in the scanner.

There are rare reports of patients having serious, long-term, adverse reactions following the administration of gadolinium contrast agents during MR imaging. However, this complication has been reported as occurring almost exclusively, in patients with severe renal impairment. This risk has been further minimized over recent years through changes in gadolinium formulations, dose, and administration methods.

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?
February 2018 to June 2022

Who is funding the study?
Duchenne UK (UK) and the National Institute for Health Research (UK)

Who is the main contact?
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Contact information

Type(s)
Scientific

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Additional identifiers

Clinical Trials Information System (CTIS)
Nil known

Integrated Research Application System (IRAS)
252541

ClinicalTrials.gov (NCT)
Nil known

Protocol serial number
CPMS 41597, IRAS 252541

Study information

Scientific Title
Defining the prevalence of minimally symptomatic/asymptomatic tachy- and bradyarrhythmias in patients with advanced cardiac dystrophinopathy (Duchenne & Becker muscular dystrophy [BMD/DMD])

Study objectives
1. The scars that form in the hearts of patients with Duchenne & Becker muscular dystrophy (BDMD) are similar in extent and architecture to those found in patients with idiopathic dilated cardiomyopathies and in patients after myocardial infarction ('heart attacks') in which sudden cardiac death is overwhelmingly due to VT/VF ('fast run-away' rhythms arising in the scarred main heart's pumping chamber)
2. In BDMD-patients, already established on standard heart medications for advanced but still asymptomatic left ventricular systolic dysfunction (weakened heart's main pumping chamber), electrical instability (ie. non-sustained ventricular tachycardia, or intermittent high-grade AV-block) will be identified by longer-term ECG surveillance

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 29/04/2019, North East – Tyne & Wear South Research Ethics Committee (NHSBT Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ; +44 (0)207 1048084; tyneandwearsouth.rec@hra.nhs.uk), ref: 19/NE/0066

Study design
Non-randomised cohort study

Primary study design
Observational

Study type(s)
Screening

Health condition(s) or problem(s) studied
Duchenne or Becker muscular dystrophy

Interventions
Participants providing informed written consent will undergo MR-imaging of heart at study entry, if a scan has not already been performed within the previous six months. Imaging will include late-Gadolinium enhanced sequences to allow scar detection, characterization, and quantification.

Image sets from these BDMD patients will be compared with scans obtained and stored previously from patients following myocardial infarction and patients with idiopathic dilated cardiomyopathy. All cardiac MR-images will be analyzed using specialist software ('CMR-42'), already available. This allows detailed quantification of scar burden, its distribution, and architecture including T1 map capability.

BDMD patients will have a loop-recorder implanted under local anaesthesia within two months of study entry. These devices have battery life for more than 3 years and record ECGs automatically using pre-defined, programmable criteria for abnormally fast or slow rhythms. In addition, patients can record an ECG at the time of any symptoms using an 'activator'. These implanted devices communicate with the hospital automatically by means of a remote monitoring system uniquely linked to each device, which allows ECG uploads of either patient-activated or automatic recordings remotely. Patients do not have to come to the hospital to download data and the device provides comprehensive rhythm surveillance. Patients will also be asked to complete quality of life questionnaires (SF-36, INQoL, or similar) at study entry and 6-monthly during follow-up. Findings will be reported after 3 and 6-months of loop-recorder data collection for each patient and correlated with left ventricular ejection fraction at study entry and extent of cardiac fibrosis.

Intervention Type
Other

Primary outcome(s)
1. Extent, distribution, and architecture of the scarring process that occurs in the hearts of patients with Duchenne or Becker muscular dystrophy (BDMD) measured from MR-imaging (late-Gadolinium enhanced sequences) of the heart using specialist analysis software at baseline or within the 6 months prior to study recruitment
2. Scar burden and scar characteristic between a BDMD cohort and cohort of patients following anterior myocardial infarction or idiopathic dilated cardiomyopathy with similar degrees of reduced left ventricular ejection fraction (15-40%) measured from MR-imaging (late-Gadolinium enhanced sequences) of the heart using specialist analysis software at baseline or within the 6 months prior to study recruitment
3. Prevalence of asymptomatic/minimally symptomatic abnormally fast or slow disturbances of heart rhythm in BDMD patients, or female gene-carriers, with reduced left ventricular ejection fraction (15-40%) measured using implanted loop recorders (Medtronic LinQ device or similar) which provide comprehensive rhythm surveillance between baseline and 6 months of device implant

Key secondary outcome(s))
1. Quality of life measured using the questionnaires Short Form Survey (SF-36), Individualized Neuromuscular Quality of Life Questionnaire (INQoL), or similar questionnaire at baseline and 6 months

Completion date
30/06/2022

Eligibility

Key inclusion criteria
1. Genetically confirmed Duchenne or Becker muscular dystrophy (BDMD) or female BDMD-mutation carriers with similar severity of left ventricular dysfunction

2. Aged ≥18 years
3. Left ventricular ejection fraction by echocardiographic assessment between 15 and 35%
4. No history or evidence of ventricular arrhythmias (syncope/pre-syncope, cardiac arrest, AV-nodal heart block, or sinus arrest)
5. Already established on appropriate cardiac medications for cardiomyopathy (typically an angiotensin-converting enzyme (ACE) inhibitor or an angiotensin receptor blocker (ARB), or a beta blocker with or without a mineralocorticoid antagonist)
6. Willing and able to undergo cardiac magnetic resonance imaging including late-Gadolinium enhanced sequences (or using similar scar detection methods). If unable to undergo cardiac magnetic resonance imaging for safety reasons (day-time ventilated, degree of muscle contractures, claustrophobia, etc.) or do not tolerate imaging, participants can be enrolled in the arrhythmia surveillance part of the protocol without having cMRI imaging.

Participant type(s)
Patient

Healthy volunteers allowed
No

Age group
Adult

Lower age limit
18 years

Sex
All

Total final enrolment
10

Key exclusion criteria
1. Uncertain aetiology of muscular dystrophy even if a similar degree of cardiomyopathy
2. Uncertainty about ability, or inability, to provide informed written consent as determined by the investigator
3. Poor quality of life due to the overall severity of condition or co-morbidities (such as depression, respiratory failure, or inadequate pain control) at the physician's discretion
4. Unlikely to comply with follow-up of their implanted ECG-loop recorder as determined by the investigator
5. Non-compliant with recommended cardiac medications for reasons other than intolerance or adverse effects

Date of first enrolment
22/08/2019

Date of final enrolment
30/06/2021

Locations

Countries of recruitment
United Kingdom

England

Study participating centre
Freeman Hospital
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Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

Funder(s)

Funder type
Government

Funder Name
Duchenne UK

Funder Name
National Institute for Health Research (NIHR) (UK)

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 and/or analysed during the current study during this study will be included in the subsequent results publication

IPD sharing plan summary

Other

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Results article		02/04/2024	04/04/2024	Yes	No
HRA research summary			28/06/2023	No	No
Other unpublished results		13/02/2023	13/02/2023	No	No
Participant information sheet		16/12/2020	29/01/2021	No	Yes
Participant information sheet	Participant information sheet	11/11/2025	11/11/2025	No	Yes