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Electrical brain stimulation with transcranial direct current (tDCS) to treat focal epilepsy in patients with mitochondrial disease (POLG mutation)

Submission date
12/11/2021

Recruitment status
Recruiting

Registration date
16/11/2021

Overall study status
Ongoing

Last Edited
24/12/2024

Condition category
Nervous System Diseases

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

Plain English summary of protocol

Background and study aims
Mitochondria are tiny structures within cells and are often referred to as ‘powerhouses’ because of their vital role in energy production. When these 'powerhouses' are not able to produce enough energy, certain organs such as brain and skeletal muscle can be affected. This can result in a diagnosis of mitochondrial disease. Along with this disease, epileptic seizures happen because of a disruption to electrical activity in the brain that affects the communication between brain and body. This can lead to a change in a person’s movement, behaviour, level of awareness and/or feelings. Focal onset epilepsy means that the seizures start in a specific part of the brain. This is often the case in people with mitochondrial disease.
To calm the epileptic seizures transcranial direct current stimulation (or tDCS) can be applied on the head and delivers a low electric current. TDCS has been successfully used to treat epilepsy in other diseases. In our clinic, we have treated focal-onset mitochondrial epilepsy with tDCS together with the standard medication and seen that symptoms improve.
With this study, we want to measure the effectiveness of tDCS for mitochondrial epilepsy in a systematic way. One study group will receive active tDCS 2 days earlier during which the other group receives non-active sham stimulation instead (called 'delayed-start’ protocol). Assignments to the study group will be randomised. Both types of stimulations, active and sham, will feel very similar. Nobody who is directly involved in the research will know the assigned study group (called ‘double-blind’).

Who can participate?
Patients aged 2 years and above, with mitochondrial disease and drug-resistant focal epilepsy.

What does the study involve?
Pre-intervention Assessments
For screening and safety purposes, the following assessments will be performed to confirm study elibility:
• Collection of medical history, demographics: We will ask questions about their medical history,

any medications they are taking and about their lifestyle (1x).
• Physical examination: A doctor will perform a general medical examination. In addition, their height, weight, heart rate, respiration rate, blood pressure and head circumference will be recorded (1x).
• Quality of life questionnaire: We will ask participants to complete two quality of life questionnaires to measure how the tDCS and potential improvement of symptoms affects their perceived satisfaction or dissatisfaction in their day-to-day living. One questionnaire will be completed before and the other one 1 week after the treatment (2x).
Daily monitoring
• Seizure diary: We will ask participants to complete a seizure diary 3x daily over the tDCS treatment period and will permission to collect any relevant clinical information from their hospital medical records. Our research team will assist with that.
• Video monitoring (optional): We would like to capture short videos (1-2 min daily) of the areas of their body affected by the seizures (either in clinic or by participant/parents/carers at the home). These videos will be anonymised (i.e. by blurring out facial features) prior to long-term storage/analysis. We will ensure that the identifiable images (i.e. prior to anonymization) are transferred securely.

Treatment
Every day for up to 14 days the following treatment steps will be performed:
• Preparation for tDCS: A neoprene cap will be placed on their head. We will prepare two cup-shaped electrodes with a conductive gel. The electrodes are placed between the cap and the scalp – one electrode over the location of the focal epileptic event (or seizure location) and another one opposite to that.
• Early-start tDCS treatment condition: Early-start involves active tDCS from day 1 onwards. For active tDCS a current will be delivered at 2 mA for 20 mins 1x daily (every 24 h). These stimulation parameters have been safely used, as reported in the relevant research literature. We apply a weak current to the site of the head where the seizures appear. Most people will feel a mild tingling, prickling, itching, or warmth during the stimulation. These sensations are not painful and go away when stimulation stops. Daily sessions continue for a period of up to 14 days (until day 14). We will stop the intervention earlier if their seizures stop before day 14. The early-start group will not receive any sham tDCS.
• Delayed-start tDCS conditions: On day 1 and 2 we will set up the tDCS device without a long-term current being delivered. The tDCS device will instead deliver a very brief weak current that feels like active stimulation, but no treatment is delivered (this is called ‘sham’). This is necessary to make sure nobody involved in the treatment and measurements will know which group they are in. From day 3 onwards participants will receive the active tDCS treatment for sure. This is to make sure everyone receives at least 12 active stimulation sessions if that is needed to resolve their seizure episode.

What are the possible benefits and risks of participating?
We cannot promise the study will help the participants personally; however, study participation may get them earlier access to the tDCS treatment and may therefore result in earlier resolution of the epoch of seizure activity. The treatment effects of tDCS on mitochondrial focal epilepsy are still to be confirmed. We hope to learn about the effectiveness of the tDCS treatment for mitochondrial disease from this research. This may help other people with the disease to receive this treatment in the future.
• The study treatments to be performed are safe and well-tolerated by most people and will be performed by experienced researchers. The National Institute for Health and Care Excellence (NICE) investigated the safety of tDCS. They published guidelines stating that tDCS raises no major safety concerns (for the treatment of depression).
• We will ensure that participants are suitable to undergo the procedure before they enter the

study, and again before each treatment.
• During the tDCS or sham stimulation, participants may experience an itching or tingling sensation, or skin redness on their scalp. Some people can experience a headache, light-headedness, drowsiness, or discomfort at the site of stimulation. However, all these effects should be mild and relatively short-lived. Before each treatment session the scalp will be inspected for any skin irritations. The medical tDCS device used during the treatment will automatically monitor good contact of the electrodes with the skin throughout all the session. This ensures a constant delivery of the current and avoids the side effects.
• Assistance with any additional travel and parking costs will be provided. We will also provide refreshments/reimbursement for the cost of light refreshments during the visit.
• Taking part in the study will mean that participants may need to be available for the stimulation treatment every day for approx. 30 mins until their symptoms resolve for a maximum of 14 subsequent days. We would ask them or their carer/ relatives to take careful notes on their seizure frequency. We will provide a form for that and explain the details of this procedure and provide assistance if needed.

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?
December 2020 to December 2024

Who is funding the study?
The Lily Foundation (UK)

Who is the main contact?

Contact information

Type(s)
Scientific

Contact name
Dr Katrin Bangel

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number
281536

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
CPMS 49769, IRAS 281536

Study information

Scientific Title
TRANscranial direct current Stimulation for FOcal Refractory epilepsy in Mitochondrial disease (TRANSFORM): delayed-start, randomised, double-blinded, placebo-controlled trial

Acronym
TRANSFORM

Study objectives
Our goal is to assess the efficacy of tDCS as an adjunctive treatment in reducing the number of focal epileptic seizures experienced by children and adults with genetically-confirmed mitochondrial disease.

Ethics approval required
Old ethics approval format

Ethics approval(s)
Approved 14/09/2021, Yorkshire & The Humber - Leeds West Research Ethics Committee (NHSBT, Newcastle Blood Donor Centre, Holland Drive, Newcastle upon Tyne, NE2 4NQ, UK; +44 (0)207 104 8088; leedswest.rec@hra.nhs.uk), ref: 21/YH/0137

Study design
Interventional randomized controlled trial

Primary study design
Interventional

Secondary study design
Randomised controlled trial

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use the contact details below to request a patient information sheet

Health condition(s) or problem(s) studied
Focal refractory epilepsy in mitochondrial disease

Interventions
At baseline, participants will be randomly assigned to receive either sham stimulation (delayed-start group) or active tDCS (early-start group). The placebo group will receive a double-blinded sham procedure for 2 days. On day 3, all patients will receive the active tDCS intervention as an adjunctive treatment for up to 14 days. To obtain sufficient recruitment the duration of the entire study will be 24 months.

Pre-intervention Assessments
For screening and safety purposes, the following assessments will be performed to determine whether study inclusion criteria are met:
• Collection of full medical history and basic demographics (name, address, date of birth, and NHS Number)
• Physical examination: General medical examination (of height, weight, heart rate, respiration rate, blood pressure, and head circumference)

Treatment
Every day the following treatment steps will be performed:
• Preparation for tDCS: A neoprene cap will be placed on the participant's head. We will prepare two cup-shaped electrodes with a conductive gel. The electrodes are placed between the cap and the scalp and connected to the device.

• tDCS treatment:
For active tDCS, a current will be delivered at 2 mA for 20 mins 1x daily (every 24 h). The negative current is applied over the seizure site (called 'cathodal stimulation'). These stimulation parameters have been safely used, as reported in the relevant research literature.
The early start group receives active tDCS from day 1 onwards.
The delayed start group receives active tDCS from day 3 onwards. Daily stimulation continues for a period of up to 14 days (until day 14). The stimulation will be stopped earlier if the focal epileptic episode resolves before day 14. We will ask participants to remain seated during the preparation and stimulation period but will be able to do activities that do not require much movement (reading, use of phone/tablet, etc.)

• Sham tDCS: Participants from the delayed start group will receive sham stimulation on day 1 and day 2. The tDCS device will deliver a very brief weak current that feels like active stimulation. This is necessary to keep participants and investigators blind to the group allocation. From day 3 onwards all participants will receive the active tDCS treatment to make sure each patient received at least 12 active stimulation sessions if that is needed to resolve the seizure episode. The early-start group will not receive any sham tDCS.

• Seizure diary: Completion of a seizure diary/collection of seizure events 3x daily over the tDCS treatment period. Research technicians, nurses etc. will assist with that.
• Quality of life questionnaires are filled out before and one 1 week after the treatment.
• Video monitoring (optional): We would like to capture short videos (1-2 min daily) of the areas of the body affected by the seizures (either in the clinic or by the patient/parents/carers at the home). This is an optional assessment, and it is possible to participate in the study without video capture.

Intervention Type

Device

Phase
Not Applicable

Drug/device/biological/vaccine name(s)
Transcranial direct current stimulation

Primary outcome measure
Seizure frequency (number and duration of seizures, jerks/min according to European Medicines Agency guidelines). This is measured by daily reporting from specialists, nurses, research staff, relatives, and carers by seizure diary and video monitoring from day 0 to day 14.

Secondary outcome measures
1. Seizure freedom (based on daily seizure diary for max 14 days, video monitoring, and end-of study EEG).
2. Adverse events measured using case report forms throughout the study.
3. Assessment of side effects by daily seizure diary.
4. Neurophysiology and/or neuroradiology findings: MRI, CT and EEG if obtained before study inclusion as part of standard care to localise the seizure are compared to measurements after the treatment. We obtain an end of study EEG and also ask permission for the patient's clinical information (e.g. MRI/CT) obtained before and up to 6 months after the study to evaluate the treatment effects
5. Quality of life assessed by validated participant and carer(s) questionnaires at baseline and after 14 days

Overall study start date
01/12/2020

Completion date
01/12/2026

Eligibility

Key inclusion criteria
1. Adult and paediatric patients aged >=2 years
2. Patients with a genetically confirmed diagnosis of mitochondrial disease
3. Drug-resistant focal epilepsy defined by the International League Against Epilepsy (ILAE) as failure of two antiepileptic drugs to achieve sustained seizure freedom
4. Anatomically relevant changes related to focal seizures defined by neuroimaging and/or scalp EEG
5. Able to undergo all study assessments and investigations in the opinion of the recruiting investigator in agreement with the patient/parents/legal guardian
6. For patients under the age of 16 years, parental consent must be provided

Participant type(s)
Patient

Age group
Mixed

Lower age limit
2 Years

Sex
Both

Target number of participants
Planned Sample Size: 30; UK Sample Size: 30

Key exclusion criteria
1. Paediatric patients aged <2 years
2. Patients with metallic implants (pins, stents, metal clips etc.) or electronic implants (e.g., pacemaker, defibrillator, cochlear implants, and other forms of stimulator) that typically preclude MRI scanning and/or tDCS treatment.
3. Patients with other co-existing epileptic comorbidity e.g., brain tumour, traumatic brain injury, cortical dysplasia
4. Patients with other known uncontrolled medical problems that, in the opinion of the investigator, would preclude participation in the study.
5. Inability of patient/legal guardian to provide informed consent.
*MRI scanning is regularly done as part of the standard clinical care of our target patient group. This study relies on the MRI results in order to determine the target for tDCS stimulation as part of the regular clinical care. No MRI exams will be performed as a part of this study.

Date of first enrolment
01/12/2021

Date of final enrolment
01/12/2026

Locations

Countries of recruitment
England

United Kingdom

Study participating centre
Freeman Hospital
Newcastle Upon Tyne Hospital Trust
Freeman Road
High Heaton
Newcastle
United Kingdom
NE7 7DN

Sponsor information

Organisation
Newcastle upon Tyne Hospitals NHS Foundation Trust

Sponsor details
Freeman Hospital
Freeman Road
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+44 (0)191 2825959
nuth.nuthsponsorship@nhs.net

Sponsor type
Hospital/treatment centre

Website
http://www.newcastle-hospitals.org.uk/

ROR
https://ror.org/05p40t847

Funder(s)

Funder type
Charity

Funder Name
The Lily Foundation

Results and Publications

Publication and dissemination plan
Planned publication in a high-impact peer-reviewed journal and conference presentation

Intention to publish date
01/12/2026

Individual participant data (IPD) sharing plan
The current data sharing plans for this study are unknown and will be 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
Protocol article		22/10/2024	29/10/2024	Yes	No