ISRCTN14292082 https://doi.org/10.1186/ISRCTN14292082

Investigating the genetic, environmental and nutritional factors associated with Tanzanian endemic optic neuropathy (TEON)

Submission date
28/08/2019

Recruitment status
Suspended

Registration date
29/04/2020

Overall study status
Completed

Last Edited
30/06/2021

Condition category
Eye Diseases

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

Plain English summary of protocol

Background and study aims
Tanzanian endemic optic neuropathy (TEON) causes irreversible vision loss in young people, resulting in significant disability and huge educational and economic implications. The condition, which is centred around the city of Dar es Salaam in Tanzania, affects up to 1 in 40 people aged 10-39 years, some 40,000 people.
Despite being a relatively common disease, the cause of TEON is still unknown.
TEON patients have varying levels of poor vision, alongside problems appreciating colours. Some patients with TEON also have hearing loss and numbness in their hands and feet. Optic neuropathy is an 'umbrella term' referring to a number of different diseases that affect the optic nerve, the nerve that takes visual information from the eye to the brain. What is known is that TEON is due to damage to the optic nerve, which connects the eye to the brain. This nerve needs a lot of energy to work properly, which means that damage to mitochondria, the portion of a cell that produces energy, can severely affect the optic nerve. TEON has similar symptoms to Leber's hereditary optic neuropathy (LHON), which is known to be due to mitochondria not functioning well. However, the genetic changes found in European patients with LHON have not been found in African patients with TEON.
Based on recent research in other fields, it is thought that TEON is the result of damage to mitochondria from a number of lifestyle (diet) and environmental (low sunlight exposure) factors in people who are genetically more likely to develop the condition. Rapid urbanisation in East Africa has led to reduced skin ultraviolet light (sunlight) exposure, combined with a carbohydrate-based diet low in protein, vitamins and other nutrients. Previous research has shown shat people with TEON have low vitamin D levels, which means it is likely they are not getting enough direct sunlight. Vitamin D influences many cellular processes, including mitochondrial functioning. In addition, recent evidence demonstrates that sunlight exposure releases nitric oxide (NO) from skin, which also affects mitochondrial function. Low folate (vitamin B9) levels, low protein diet and exposure to indoor cooking fumes have also been shown to be associated with TEON but so far this has not led to an effective prevention or treatment.
This is a pilot study aiming to understand more about the causes of TEON. The researchers plan to assess what went well and not so well from this study to help plan a larger-scale study that

would aim to establish the causes of TEON. Ultimately the aim is that this research will lead to an effective strategy to prevent this significant cause of visual impairment in young adults. It is also hoped that this project will encourage local involvement in research.

Who can participate?
People aged 10-34 years in Dar es Salaam who have been recently diagnosed with TEON and have not received any treatment. The study will also recruit people aged 10-34 years who are healthy for comparison.

What does the study involve?
There is one visit to the clinic. Participants will be asked about their lifestyle (such as exposure to sunlight, cooking and dietary details, education, occupation and family history). They will have an eye examination, eye scans, a hearing test, a colour vision test and an examination of nerve function in their hands and feet. A sample of blood will be taken to investigate their genetic make-up and levels of vitamins and other substances that might be raised or lowered in TEON.

What are the possible benefits and risks of participating?
Participants might benefit from having a complete eye examination. There is the possibility that previously unknown health condition will be discovered when taking part in the study. In this situation a referral to the appropriate healthcare provider would be made. Participants may experience some pain or discomfort when the blood sample is taken.

Where is the study run from?
University of St Andrews (UK)

When is the study starting and how long is it expected to run for?
July 2019 to February 2022

Who is funding the study?
Fight for Sight (UK)

Who is the main contact?
Dr Frederick Burgess, frb2@st-andrews.ac.uk

Study website
https://med.st-andrews.ac.uk/medicine/tanzanian-endemic-optic-neuropathy/

Contact information

Type(s)
Public

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Additional identifiers

EudraCT/CTIS number
Nil known

IRAS number

ClinicalTrials.gov number
Nil known

Secondary identifying numbers
24RCO5

Study information

Scientific Title
Tanzanian Endemic Optic Neuropathy (TEON): A pilot case control study of genetic, nutritional and environmental determinants.

Acronym
TEON

Study objectives
This study aims to assess the genetic, nutritional and environmental risk factors associated with Tanzanian Endemic Optic Neuropathy (TEON). The aim is to understand the pathophysiology of TEON in more detail, with a view to developing effective interventions that will lead to a reduction in the disease burden in East Africa.

Objectives of pilot study:
1. Perform a case control study exploring the associations of lifestyle (with a focus on diet and sun exposure), genetics (known optic neuropathy disease-causing genes) and biochemical status (micro-nutrients and redox status) with TEON
2. Obtain experience of research on TEON in Dar es Salaam, thereby testing data collection methods to inform larger scale studies

Ethics approval required
Old ethics approval format

Ethics approval(s)
1. Approved 27/08/2019, University of St Andrews University Teaching and Research Ethics Committee (Medical and Biological Sciences Building, North Haugh, St Andrews, Fife, KY16 9TF, UK; +44 (0)1334 463585; medethic@st-andrews.ac.uk), ref: MD14540
2. Approved 12/11/2019, Muhimbili University of Health and Allied Sciences Senate Research and Publications Committee (PO Box 65001, Dar es Salaam, Tanzania; +255 22 2152489; sunguya@gmail.com), ref: DA.282/298/01.C/

3. Approved 20/11/2019, National Institute of Medical Research (3 Barack Obama Drive, PO Box 9653, 11101 Dar es Salaam, Tanzania; +255 22 2121400; nimrethics@gmail.com); ref: NIMR/HQ/R.8a/Vol.IX/3271
4. Approved 10/12/2019, Muhimbili National Hospital (PO Box 65000, Dar es Salaam, Tanzania; +255 22 2151367; no email), ref: MNH/TRCU/IRB/Permission/2019/255
5. Approved 12/12/2019, Comprehensive Community Based Rehabilitation in Tanzania Hospital Ophthalmology Department (PO Box 23310, Dar es Salaam, Tanzania; +255 222602192; communications@ccbrt.org), no reference number

Study design
Observational multicentre case-control study.

Primary study design
Observational

Secondary study design
Case-control study

Study setting(s)
Hospital

Study type(s)
Treatment

Participant information sheet
Not available in web format, please use contact details to request a participant information sheet.

Health condition(s) or problem(s) studied
Tanzanian endemic optic neuropathy (TEON)

Interventions
Schedule of procedures:
Referral: by initial ophthalmologist to Dr Burgess, after first presentation to hospital eye services.

Screening: performed by Dr Burgess, at the site of their initial presentation ('the recruitment site').
1. Eligibility assessment (taking a medical history) - 30 min
2. Consent - 15 min

Post-screening visit: performed by Dr Burgess, at Muhimbili National Hospital.
1. Questionnaire (sunlight exposure, occupation, education, address, diet, cooking habits, smoking status, alcohol intake, family history of eye disease) - 30 min
2. Visual acuity measurement - 1 min
3. Colour vision assessment - 1 min
4. Blood pressure measurement (sphygmomanometer) - 2 min
5. Ophthalmic (pupils, slit lamp) examination - 15 min
6. Intra-ocular pressure measurement (Goldmann applanation tonometry) - 2 min
7. Cranial nerve examination - 3 min
8. OCT scan - 3 min

9. Neurological examination - 5 min
10. Audiometry - 5 min
11. Blood tests (venepuncture) - 5 min

Intervention Type
Not Specified

Primary outcome measure
1. Biomarkers of oxidative stress assessed by measuring levels of the following in blood of patients with TEON at baseline:
1.1. NO metabolites (nitrite, nitrate, RXNO)
1.2. H2S metabolites (sulfide, sulfate)
1.3. Redox regulation (total free thiols, free and bound LMW thiols [cysteine, glutathione, homocysteine], ascorbate/dehydroascorbate and 4-hydroxynonenal [4-HNE])

Secondary outcome measures
1. Presence of genetic mutations known to be associated with optic neuropathy in patients with TEON via peripheral venous blood sampling at baseline in both cases and first-degree relative controls
2. Serum level of vitamin D in blood of patients with TEON at baseline
3. Serum level of vitamin B12 in blood of patients with TEON at baseline
4. Serum level of thiamine in blood of patients with TEON at baseline
5. Sunlight exposure of patients with TEON assessed using a questionnaire at baseline

Overall study start date
07/07/2019

Completion date
06/02/2022

Eligibility

Key inclusion criteria
Case group:
1. Signed written consent from all participants, prior to undertaking any study procedures
2. Aged 10-34 years
3. The case definition of TEON, as per previous studies, is a bilateral optic neuropathy of subacute, progressive onset with best-corrected visual acuities of 6/9 or worse in both eyes, alongside an acquired colour vision deficiency, in the presence of temporal optic disc pallor (with OCT evidence of corresponding thinning) or optic disc hyperaemia
4. Cases who meet the case definition and have been referred to the Eye Units in Dar es Salaam for further assessment

Control group:
1. Signed written consent from all participants prior to undertaking any study procedures
2. Aged 10-34 years
3. Participants who have had an ophthalmic history, examination and screening and satisfy the classification criteria for not being diagnosed with TEON
4. Controls will, where possible, be first-degree relatives of a case group participant

Participant type(s)

Mixed

Age group
Mixed

Sex
Both

Target number of participants
60

Key exclusion criteria
1. Cataract in either eye
2. History of ocular trauma
3. Diagnosis of another ocular pathology except refractive error
4. Relative afferent pupillary defect
5. Signs and symptoms suggestive of raised intracranial pressure
6. Existing diagnosis of multiple sclerosis (or any other demyelinating condition)
7. Untreated hypertension
8. Unilateral disease
9. Significant needle phobia
10. Use of oral vitamin supplements
11. Use of amiodarone, linezolid, ethambutol, isoniazid, tetracycline spp, oral chloramphenicol, methotrexate, lithium, metronidazole or omeprazole

Date of first enrolment
13/12/2019

Date of final enrolment
06/02/2022

Locations

Countries of recruitment
Tanzania

Study participating centre
Muhimbili National Hospital
United Nations Road
Dar es Salaam
Tanzania
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Study participating centre
Dr Agrawal's Eye Hospital
4th floor Faykat Towers
Kinondoni

Dar es Salaam
Tanzania
8964

Study participating centre
CCBRT Hospital
PO Box 23310
Dar es Salaam
Tanzania
-

Sponsor information

Organisation
University of St Andrews

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Sponsor type
University/education

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ROR
https://ror.org/02wn5qz54

Funder(s)

Funder type
Charity

Funder Name
Fight for Sight UK

Alternative Name(s)
Fight for Sight

Funding Body Type
Private sector organisation

Funding Body Subtype
Trusts, charities, foundations (both public and private)

Location
United Kingdom

Results and Publications

Publication and dissemination plan
The funder will be acknowledged within the publications and will review the publication rights of the data from the study. The participant will not be able to request results from their principal investigators after the final study report has been compiled or after the results had been published. The dissemination of results will be through the scientific reviewed press to participants, practitioners and policy makers.

Intention to publish date
01/01/2021

Individual participant data (IPD) sharing plan
Data from the study will be owned by The University of St Andrews, as the host institution. On completion of the study, the data will be analysed and tabulated and a final study report prepared. The full study report will be deposited in the University of St Andrew's PURE data repository. Only fully anonymised data will be stored and will only be accessible to the research team (as per Tanzanian data law). As per the collaboration agreement, each institution will grant to the other a perpetual, non-exclusive, worldwide, royalty-free, non-transferable licence to use the other institution's results for their own internal research and teaching activities. The anonymised participant level dataset and statistical code for generating the results will not be made publicly available.

IPD sharing plan summary
Stored in repository

Study outputs

Output type	Details	Date created	Date added	Peer reviewed?	Patient-facing?
Other publications	OCT findings	01/09/2020	30/06/2021	Yes	No