

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

Submission date 28/08/2019	Recruitment status Suspended	<input type="checkbox"/> Prospectively registered <input type="checkbox"/> Protocol
Registration date 29/04/2020	Overall study status Completed	<input type="checkbox"/> Statistical analysis plan <input type="checkbox"/> Results
Last Edited 30/06/2021	Condition category Eye Diseases	<input type="checkbox"/> Individual participant data <input type="checkbox"/> 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 that 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

Contact information

Type(s)

Public

Contact name

Dr Frederick Burgess

ORCID ID

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Additional identifiers

Clinical Trials Information System (CTIS)

Nil known

ClinicalTrials.gov (NCT)

Nil known

Protocol serial number

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@cbrt.org), no reference number

Study design

Observational multicentre case-control study.

Primary study design

Observational

Study type(s)

Treatment

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(s)

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])

Key secondary outcome(s)

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

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

Healthy volunteers allowed

No

Age group

Mixed

Sex

All

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

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Sponsor information

Organisation

University of St Andrews

ROR

<https://ror.org/02wn5qz54>

Funder(s)

Funder type

Charity

Funder Name

Fight for Sight UK

Alternative Name(s)

Fight for Sight, Fight for Sight (UK)

Funding Body Type

Private sector organisation

Funding Body Subtype

Trusts, charities, foundations (both public and private)

Location

United Kingdom

Results and Publications

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

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

[Study website](#)

Study website

11/11/2025

11/11/2025

No

Yes