Identifying Primary Open Angle Glaucoma Patients with Mitochondrial Dysfunction

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Main objectives: 1. Determine whether the POAG patients with low values of the blood mtDNA copy number have a low mtDNA copy number and low mitochondrial function in skin fibroblasts, using in vitro assays of mitochondrial function.2. Explore the...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Glaucoma and ocular hypertension
Study type	Observational invasive

Summary

ID

NL-OMON53359

Source
ToetsingOnline

Brief title
Mitochondrial dysfunction in POAG patients

Condition

- Glaucoma and ocular hypertension

Synonym
glaucoma, primary open angle glaucoma

Research involving
Human

Sponsors and support

Primary sponsor: Medisch Universitair Ziekenhuis Maastricht
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: blood biomarker, fibroblast, glaucoma, mitochondrial dysfunction

Outcome measures

Primary outcome

Mitochondrial DNA copy number and mitochondrial function measured in in vitro assays of skin fibroblasts, compared between control (group 1) and POAG with low blood mtDNA copy number (group 2).

Correlation between mitochondrial DNA copy number in the blood and mitochondrial function measured in fibroblasts within the POAG group (group 3).

Secondary outcome

1. Effects of drugs on mitochondrial function as determined in fibroblast assays.

In case that we can identify POAG patients with lower mitochondrial function than controls in a fibroblast assay, we will use this in vitro assay to test whether mitochondrial enforcing drugs can improve mitochondrial function in these fibroblasts assays. Dose-response curves will be established.

2. Explore the potential value of (additional) blood biomarkers for identifying POAG patients with mitochondrial dysfunction.

After we have measured mitochondrial dysfunction with the gold standard method of functional assays in fibroblasts, we can use these data to document the relation between blood (or blood cell) biomarkers and the status of mitochondrial function. Besides the blood cell mtDNA copy number which has been determined before, these biomarkers include blood metabolomics analysis of

metabolites of mitochondrial function (e.g. nicotinamide) and mitochondrial outer membrane potential measurement in peripheral blood mononuclear cells (PBMCs) as measured by TMRM staining.
To assess the value of these blood biomarkers, we will calculate the relationship between the blood biomarker with the mitochondrial parameters measured in the fibroblast assays.

3. Further characterization of mitochondrial function.
To reveal additional differences between POAG and control subjects, additional functional assays of mitochondrial function can be performed with the fibroblasts (e.g. Seahorse XF analysis).

4. Characterization of genetic variants
DNA sequencing will be performed to study the possible association of genetic variants with mitochondtrial dysfunction and with POAG.

Study description

Background summary

Primary Open-Angle Glaucoma (POAG) is a heterogeneous, multifactorial disorder. Research data increasingly support the hypothesis that, at least in some POAG patients, suboptimal mitochondrial function plays a role in the pathophysiology. If we can identify these patients, we can examine whether they can benefit from drugs that bolster mitochondrial function.
Since taking an optic nerve biopsy to measure local mitochondrial function is not possible, we tried to measure mitochondrial dysfunction indirectly by blood biomarkers, such as the blood cell mitochondrial DNa (mtDNA) copy number. This is a valid strategy since we are looking for genetic predisposition, which should be apparent in all body cells. Screening for this biomarker revealed

that POAG patients, on average, have lower mtDNA copy number. This lower mtDNA copy number could mean that the mitochondria are not working well and suggests that mitochondria may play a role in glaucoma. This is tested in the current study in which we will use skin fibroblasts to measure mitochondrial function in detail in a small group of patients, selected based on the level of the biomarker in their blood. We also want to explore whether this blood biomarker can be useful for identifying the POAG patients with mitochondrial dysfunction.

Study objective

Main objectives:
1. Determine whether the POAG patients with low values of the blood mtDNA copy number have a low mtDNA copy number and low mitochondrial function in skin fibroblasts, using in vitro assays of mitochondrial function.
2. Explore the relation between blood mtDNA copy number and fibroblast mitochondrial function within the POAG group in order to assess whether the blood mtDNA copy number could become a diagnostic biomarker identifying POAG patients with low mitochondrial function within the POAG group.

Secondary objective:
1. If we are able to identify POAG patients with low mtDNA copy number and low mitochondrial function, we will employ the in vitro assays to screen for compounds that improve mitochondrial function in vitro in these patients* fibroblasts.
2. Based on the measurement of mitochondrial function in fibroblasts assays as *gold standard* method, we will assess additional blood biomarkers for identifying POAG patients with mitochondrial dysfunction.
3. Further characterization of mitochondrial function using fibroblasts assays aiming to find additional differences related to POAG.
4. Genetic analysis of mitochondrial genes, especially those involved in mtDNA replication given the reduced copy number, to identify the underlying genetic cause or risk factors.

Study design

Mono-center, observational study using biomaterial (skin biopsy, blood).

From each participant, a skin biopsy (3 mm) and a 20 ml fasting, venous blood will be collected during a single visit to the clinic.

Study burden and risks

Participants will visit the Maastricht UMC only one time. During this visit, we will collect a skin biopsy (~ 3 mm in diameter) and a (>3 hr) fasting blood sample (20 ml).
Blood collections and punch skin biopsies are routinely performed in the

clinic. They may be painful in some cases. Infections and bleeding afterwards are possible, but rare. To minimize patient burden of the skin biopsy, local anaesthesia will be applied. The burden for the participants is balanced by the possible benefit to develop neuroprotective treatments for POAG patients with mitochondrial dysfunction.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

The source population is the population of the participants of the Eye Tissue Bank Maastricht (ETBM). The ETBM is open for all glaucoma and cataract patients of the University Eye Clinic Maastricht to participate. In general, this is an elderly (glaucoma and cataract), Caucasian population inhabiting the south of Limburg.

From the population of the ETBM, we previously selected the 175 participants of the blood biomarker study: POAG patients and controls.
From these 175 participants of the blood biomarker study, we now select 3 study groups for the current study.

4.2 Inclusion criteria

The blood biomarker study included 175 participants, POAG and Control from the ETBM with the following criteria:

Inclusion criteria of the biomarker study:
- POAG group: Well-documented diagnosis of POAG.
- Control group: Well-documented ophthalmic history without glaucoma.
- Over 18 years old

Additional inclusion criteria of the current METC research proposal:
- Group 1: POAG patients with lowest values of mtDNA copy number in blood cell DNA
- Group 2: POAG patients, randomly selected
- Group 3: Control patients, randomly selected; without glaucoma.

We aim to collect fibroblast cell lines from 15 individuals per group. We expect to need skin biopsies from 15 to max 18 persons per group to achieve this. We will try to select these from the participants of the previous blood biomarker study. However, it will not be possible to include sufficient participants (15 to max 18) from the control group of the blood biomarker study to reach the required number of 15 individual fibroblast cell lines for the control group of the current study. To complete the required number for this group we will include additional control participants who we select directly (and randomly) from the source population (Eye Tissue Bank Maastricht), applying all appropriate inclusion and exclusion criteria of this control group and applying the age range which is present in the other (POAG) study groups of the current study.

Exclusion criteria

Exclusion criteria of the blood biomarker study:
- Systemic diseases in which mitochondria may be involved.
- Use of drugs that affect mitochondrial function.

Additional exclusion criteria of the current METC research proposal:
- No informed consent
- Use of oral anti-coagulants
- Significant concurrent disease e.g., cancer, diabetes, neurological disorders (except for glaucomatous disorders), heart-related disorders, blood/platelet

disorders or other diseases affecting the liver, kidney (except kidney stones) or the lungs (except bronchitis).
- inherited metabolic disorder will be used as exclusion criterium for group 1 and 3, and as variable for group 2
- Other concurrent eye diseases e.g., uveitis, age-related macular degeneration or diabetic retinopathy.
- Ongoing participation in other clinical trials that contain an intervention.
- Any other factor that in the opinion of the investigator excludes the patient from the study.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	11-09-2024
Enrollment:	54
Type:	Actual

Medical products/devices used

Registration:	No

Ethics review

Approved WMO

Date:	18-07-2023
Application type:	First submission

Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	27-05-2024
Application type:	Amendment
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
CCMO	NL83466.068.23