High-field (7T) MRI biomarkers for neurocognitive impairment in MELAS and the role of diabetes.

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Primary Objectives: 1. To tailor and apply multi-parametric, functional MRI techniques to identify cerebral abnormalities (cerebral biomarkers) in MELAS patients.2. To investigate which cerebral biomarkers are shared and differ between MELAS...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metabolic and nutritional disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON41572

Source
ToetsingOnline

Brief title
7T MRI in MELAS

Condition

- Metabolic and nutritional disorders congenital
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym
brain structure, cognition

Research involving
Human

Sponsors and support

Primary sponsor: Universiteit Maastricht
Source(s) of monetary or material Support: STW P11-41

Intervention

Keyword: Cognition, Diabetes Mellitus type 2, Imaging, MELAS

Outcome measures

Primary outcome

MRI Biomarkers of brain alterations, including:

• Quantitative measures (T1/T2* relaxation times),

• Cerebral blood flow (arterial spin labeling, ml blood/100 g tissue/min),

• Functional characteristics (in resting state or during a task),

Secondary outcome

Cognitive functioning z-scores based on different domains:

• Memory,

• Mental speed,

• Attention and executive functioning,

• Visual and spatial abilities

Study description

Background summary

Mutations in the mitochondrial DNA (mtDNA; containing 37 genes encoding for 13 proteins) underlie severe multisystem (mitochondrial) disorders (MID). An example of a mitochondrial mutation associated with a MID is the A to G transition at nucleotide 3243 of the mitochondially encoded transfer RNA leucine 1 (MT-TL1) gene (m.3243A>G). Patients that carry the m.3243A>G mutation are highly associated with the development of mitochondrial encephalomyopathy with lactic acidosis and stroke-like episodes (MELAS) syndrome. Besides these symptoms, cognitive impairment is frequently diagnosed during the course of the disease, parallel to worsening of cerebral abnormalities (e.g. brain atrophy and stroke-like lesions). Additionally, MELAS is often related to an increased prevalence of diabetes. Nearly 100% of all carriers of the m.3243A>G mutation develop diabetes before the age of 70. Like MELAS, diabets mellitus 2 (DM2) is

associated with accelerated cognitive decline and dementia in older individuals. MRI visible abnormalities associated with DM2 include atrophy, white matter lesions, and silent lacunar infarcts.

The exact neuronal mechanisms underlying the cognitive decline associated with MELAS and DM2 still remain to be elucidated. Therefore, we propose a research protocol in which anatomical, CBF and fMRI data will be acquired using high-field (7T) MRI in 26 MELAS patients with and without diabetes. Multiparametric high-field MRI will enable us to measure functional, micro-structural, micro-vascular, and metabolic changes in the effected brain.

Identification of patients* characteristics (e.g. DM2, m.3243A>G mutation load and MRI biomarkers) that may predict the onset of cognitive impairment and dementia may further optimize the current treatment of this subgroup of patients.

Study objective

Primary Objectives:
1. To tailor and apply multi-parametric, functional MRI techniques to identify cerebral abnormalities (cerebral biomarkers) in MELAS patients.
2. To investigate which cerebral biomarkers are shared and differ between MELAS patients with and without diabetes.
3. To assess whether these cerebral biomarkers and mutation load are associated with cognitive decrements in MELAS patients using multivariate analysis.

Secondary Objectives:
1. To explore the feasibility of linking high resolution neuroimaging markers, cognitive impairment and specific genetic variants in DM2.

Study design

Cross-sectional observational study

Study burden and risks

The patients/participants do not benefit from the experiment. The burden for patients/participants is restricted to 30 minutes preparation/aftercare, one high-field (7T) MRI scan session of approximately 60 minutes and one session of neuropsychological tests of approximately 30 minutes. In addtion to this, urine will be collected and blood will be drawn twice for glucose level detection using a finger prick. All the measurements are non-invasive and participants with contraindications for MRI will be excluded. Therefore the risks associated with participating in this study are negligible.

Contacts

Public
Universiteit Maastricht

Oxfordlaan 55
Maastricht 6229 EV
NL
Scientific
Universiteit Maastricht

Oxfordlaan 55
Maastricht 6229 EV
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

General:
Subjects aged 18 to 45 and subjects gave written informed consent.;MELAS patients:
Confirmed carrier of the m.3243A>G mutation and mild MELAS phenotype (fatique, myopathy, mild exercise intolerance).;Diabetes type 2:
Fasting blood glucose >= 7.0 mmol/l and/or used oral glucose-lowering medication or insulin.;Age, gender and level of education matched controls:
Those that do not carry the m.3243A>G, the age, gender and level of eduction of the group of healthy controls should not differ significantly from the age of the group of patients

Exclusion criteria

All groups:
Contra-indications for MRI examination: 1) pacemaker, 2) neurostimulator, 3) medication pump, 4) cochlear or hearing implant, 5) tattoos or other items that cannot be removed and include metal parts, 6) metal splinter in the eye, 7) pregnancy, 8) claustrophobia, 9) brain vessel clamps, 10) denture, which contains magnets, 11) operations in the past, where metal or synthetic material is used and still were in the body; psychiatric or other disorders likely to impact on informed consent; diabetes mellitus type 1 (DM1).;MELAS patients:
Other mitochondrial/neurological/psychiatric disease/syndrome other than MELAS. Severe phenotype (stroke-like lesions and severe exercise intolerance).;Age, gender and level of eduction matched controls:
Any mitochondrial/neurological/psychiatric disease/syndrome.

Study design

Design

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	13-01-2015
Enrollment:	52
Type:	Actual

Ethics review

Approved WMO

Date:	18-08-2014

Application type:	First submission
Review commission:	METC academisch ziekenhuis Maastricht/Universiteit Maastricht, METC azM/UM (Maastricht)
Approved WMO Date:	11-05-2015
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	NL47290.068.14