The diagnostic value of Metabolic Hyperspectral Imaging of the Retina in Alzheimer's disease (MHIRA).

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Neurological disorders of the eye
Study type	Observational invasive

Summary

ID

NL-OMON55124

Source
ToetsingOnline

Brief title
MHIRA

Condition

- Neurological disorders of the eye

Synonym
Alzheimer's Disease, dementia

Research involving
Human

Sponsors and support

Primary sponsor: Vrije Universiteit Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,Optina Diagnostics,VUmc fonds;Alzheimercentrum en Optina Diagnostics Inc.

Intervention

Keyword: Alzheimer's Disease, Amyloid-beta, reflectance hyperspectral retinal images, Retina

Outcome measures

Primary outcome

The diagnostic performance of MHRC by determining the sensitivity and

specificity using amyloid status, measured with amyloid PET as reference.

Secondary outcome

1. Correlation of MHRC results to syndrome diagnosis (subjective cognitive

complaints, mild cognitive impairment (MCI) or dementia) and established AD

biomarkers in CSF on brain MRI as well as cognitive performance in predicting

the amyloid status, measured with amyloid PET as reference.

2. Correlation of MHRC results to multimodal imaging of the retina, i.e.

OCT(-A) and widefield fundus photography in predicting the amyloid status,

measured with amyloid PET as reference.

3. Correlation of MHRC results to possible AD biomarkers as measured in tears

in predicting the amyloid status, measured with amyloid PET as reference.

Study description

Background summary

The human brain and retina both arise from the diencephalon during embryonic development and possess many similarities in terms of cellular structure and function. As such, there are a number of potential ocular manifestations, that may mirror Alzheimer*s disease (AD) hallmark pathology in the brain, increasing interest in imaging the retina as a potential biomarker for AD.
Recently, spectral changes were reported in Alzheimer*s mice relative to age-matched wild-type mice ex vivo and in vivo using reflectance hyperspectral

retinal images. A similar trend was observed in human brain and retina tissue post mortem. These results support the idea that hyperspectral retinal imaging could be used to identify signs of AD without an extraneous labeling agent.
The MHRC makes it possible to identify and quantify specific biomolecules in the retina, thus paving the way for metabolic imaging of the fundus. The ocular fundus image acquisition time is a few seconds. Hence, this technique permits direct, non-invasive and inexpensive evaluation of the retina without radiation. We aim to evaluate the MHRC in a large group of subjects to determine whether imaging of the retina with the MHRC may be used to predict cerebral amyloid-β status, with acceptable accuracy, using amyloid PET status for validation.

Study objective

Primarily, to investigate the diagnostic accuracy of the MHRC for predicting cerebral amyloid pathology (as measured with amyloid PET as a reference).

Secondarily, we will relate the MHRC scans to:
1. Syndrome diagnosis (subjective cognitive complaints, mild cognitive impairment (MCI) or dementia) and established AD biomarkers in CSF on brain MRI as well as cognitive performance.
2. (Widefield) fundus photography and Optical Coherence Tomography (OCT).
3. Possible AD biomarkers as measured in tear fluid.

Study design

This is an observational, prospective monocenter study. Patients will undergo a general ophthalmological consultation comprising ophthalmological history, intraocular pressure and refraction/visual acuity measurement. Based on the data of this prescreening patients will be in- or excluded.
The study comprises of 1 visit that takes place at the outpatient ophthalmology department of the AUMC, location VUmc with a duration of approximately 90 minutes.
Participants who are considered eligible after prescreening will undergo imaging with the MHRC, OCT(-A) (Heidelberg Engineering, Heidelberg, Germany and Zeiss Plexelite), and wide field fundus photography (Optos). In addition, tear fluid will be collected from both eyes.
Participants recruited from the AMYPAD-DPMS study (METc 2018.37) will undergo their study visit subsequently to the neuropsychological examination at the clinical visit of the AMYPAD-DPMS study at 6 months, ±14 days or at the clinical visit at 13 months ±4 weeks.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness (if applicable):
The study visit at Amsterdam University Medical Center (AUMC), location Vrije Universiteit Medical Center (VUmc) will take approximately 90 minutes, including a general ophthalmological examination, Optical Coherence Tomography (-Angiography) (OCT-(A)), (wide-field) fundus photography and MHRC imaging. In addition tearfluid from both eyes will be collected. In order to enhance imaging quality, participants will undergo pupil mydriasis achieved by tropicamide 0,5%, causing temporary photophobia and blurred view. These procedures are medical routine procedures; therefore, the risks are negligible. The MHRC visible light exposure is below recommended exposure limits, therefore the risks are negligible.

Benefits and risks assessment, group relatedness:
Incapacitated participants will not be included in this study. All participants have to be mentally competent, i.e. MMSE >= 17. All participants undergo an ophthalmological consultation free of charge. There are no other direct benefits for participants in this study, besides that the results obtained could lead to a simpler and less invasive method for diagnosing AD in the future.

In order to enhance imaging quality, participants will undergo pupil mydriasis achieved by tropicamide 0.5%. This is a standard procedure in ophthalmological clinical practice. Pupil mydriasis may cause transient photophobia and blurred view for several hours. Therefore, we advise participants not to drive after this examination. Mydriasis using tropicamide 0.5% can precipitate acute angle closure glaucoma in a very small proportion of cases (0.03%)24,25. Each participant will undergo ophthalmological screening to reduce this risk to be negligible and will be monitored during mydriasis. In the rare case of acute angle closure glaucoma participants will receive standard care following international glaucoma guidelines26.
The MHRC is a research device and thus does not have a CE-marking yet. Nevertheless, the MHRC meets all the safety requirements (see IMDD). The method of obtaining images and the light intensity during the procedure is comparable with the conventional fundus camera. The MHRC uses visible light exposure to the eye, and the power of the monochromatic light source has been calculated and found to be below the recommended exposure limits of the *American National Standard for safe use of lasers*1 We therefore expect the risks to patients undergoing measurements to be negligible.
The measurement of vision, intraocular pressure, fundus photography and OCT(-A) are non-invasive measurements and are all standard procedures in ophthalmological clinical practice. Risks or side effects have not been described and are not expected from these tests. Tears are sampled using paper Schirmer strips that are gently placed behind the lower eyelid. This procedure is not considered uncomfortable. In some cases, insertion of the paper strip causes reflex tearing (excessive tearing similar to tearing in reaction to

foreign body, smoke or onions).
In conclusion, risks associated with participation in the MHIRA-study are negligible.

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

- Aged 50-90 years
- Participant had amyloid PET scan preferably within 1 year of inclusion in this study
- Mini mental state exam >17 (i.e. patients are mentally competent)

Exclusion criteria

* Pupil dilation inadequate or contraindicated.
* Presence of glaucoma, retinal vascular occlusion or retinopathy (diabetic, hypertensive).
* Presence of moderate / late stage age-related macular degeneration.
* Media opacities (cataract) precluding a good quality imaging
* Refractive error outside the range -6 D to +6 D.
* Inability to obtain good quality images with the MHRC.
* Ocular conditions that could influence tear biochemical parameters (including eye infection, eye inflammation, eye surgery within the last 28 days or other acute eye conditions).

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):	08-07-2021
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO

Date:	10-07-2020
Application type:	First submission

Review commission:	METC Amsterdam UMC
Approved WMO Date:	23-08-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC

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	NL70896.029.19