Protocol Full Title prospective observational trial:

Optical coherence tomography in cerebral amyloidosis

Protocol Acronym/short title:

OCT in cerebral amyloidosis ("OCT in cerebrale amyloidose")

Version and date of protocol:

v1.1 17-04-2016

Sponsor:

Name: UZLeuven
Address: Herestraat 49, 3000 Leuven

Principal Investigator:

Name: prof. dr. Evelien Vandewalle
Address: Kapucijnenvoer 33, campus Sint-Rafaël, dienst oftalmologie, 3000 Leuven
Telephone: +32 16 34 25 09
Email: evelien.vandewalle@uzleuven.be

Sub-investigator:

Name: prof. dr. Ingeborg Stalmans
Address: Kapucijnenvoer 33, campus Sint-Rafaël, dienst oftalmologie, 3000 Leuven
Telephone: +32 16 33 23 72
Email: ingeborg.stalmans@uzleuven.be

Name: prof. dr. Rik Vandenberghe
Address: Herestraat 49, dienst neurologie, 3000 Leuven
Telephone: +32 16 3 44280
Email: rik.vandenberghe@uzleuven.be

Signatures

Principal Investigator

29/04/2016
Date

Prof. dr. Evelien Vandewalle

Sub- Investigator

29/04/2016
Date

Prof. dr. Ingeborg Stalmans

Prof. Dr. Rik Vandenberghe
Neurologie
1-34552-81-770

Sub- Investigator

26/4/2016
Date

Prof. dr. Rik Vandenberghe

Table of Contents

1. Study Synopsis

Title of clinical trial	Optical coherence tomography in cerebral amyloidosis
Protocol Short Title/Acronym	OCT in cerebral amyloidosis ("OCT in cerebrale amyloidose")
Sponsor name	UZLeuven
Principal Investigator	Prof. Dr. Evelien Vandewalle
Medical condition or disease under investigation	Community-recruited cognitively intact older adults (Control), patients with Alzheimer's Disease (AD), Lewy Body Dementia (LBD) and Mild Cognitive Impairment (MCI)
Purpose of clinical trial	To explore the distribution of novel optical coherence tomography (OCT) parameters in patients with different subtypes of dementia, MCI patients with or without positive amyloid scan and cognitively intact older adults and to evaluate the diagnostic value of these parameters.
Primary objective	Relative distribution of retinal and choroidal thickness, flow index and vessel density in the different subpopulations.
Secondary objective (s)	- Diagnostic performance of the aforementioned parameters to distinguish the different subpopulations. - The association between these parameters and the presence of cardiovascular risk factors.
Trial Design	Observational, cross-sectional
Endpoints	The diagnostic performance of retinal and choroidal thickness, flow index and vessel density to classify between amyloid positive vs amyloid negative

	controls, amyloid-positive vs amyloid negative MCI, AD and DLBD.
Sample Size	85 -15 amyloid-positive and 15 amyloid-negative cognitively intact controls (55-80 years) - 15 amyloid-positive and 15 amyloid-negative MCI patients - 15 patients in the dementia stage of AD - 10 patients with LBD
Summary of eligibility criteria	Confirmed diagnosis of MCI, AD, LBD or absence of dementia (cfr 4.1 inclusion criteria) Capable and willing to participate
Maximum duration of treatment of a Subject	/
Version and date of final protocol	V1.1 17-04-2016
Version and date of protocol amendments	

2. Background and rationale

Being a direct extension of the central nervous system and the only place in the human body where the vessels of the central circulation can be visualized directly, the eye provides a unique window to investigate the central circulatory system. Several studies have demonstrated that retinal blood vessels show structural and functional alterations in patients with dementia. These measurements are based on fundus pictures and are hence limited to the larger retinal vessels.
Until recently, intravenous injection of a contrast agent was necessary to visualize the retinal microvasculature in detail. While indispensable for the diagnosis of some ocular vascular diseases (arterial/venous occlusion, neovascularization,…) the invasiveness of fluorescein angiography (and the risk of an allergic reaction) limits its use as a screening tool to detect alterations in the microvascular network of the retina and choroid.
Optical coherence tomography (OCT) is a non-invasive diagnostic tool capable of generating cross-sectional coupes of the retina and choroid. Novel algorithms allow to render a 3-dimensional model of the ocular microcirculation based merely on the motion contrast of the circulating blood. Since OCT is fast, easy to perform and completely non-invasive, this technique lends itself for screening purposes.

The proposed study aims to investigate whether retinal or choroidal vascular parameters measured using OCT could be useful to identify different subpopulations of cognitive intact, MCI and dementia patients.

Figure 1. OCT camera

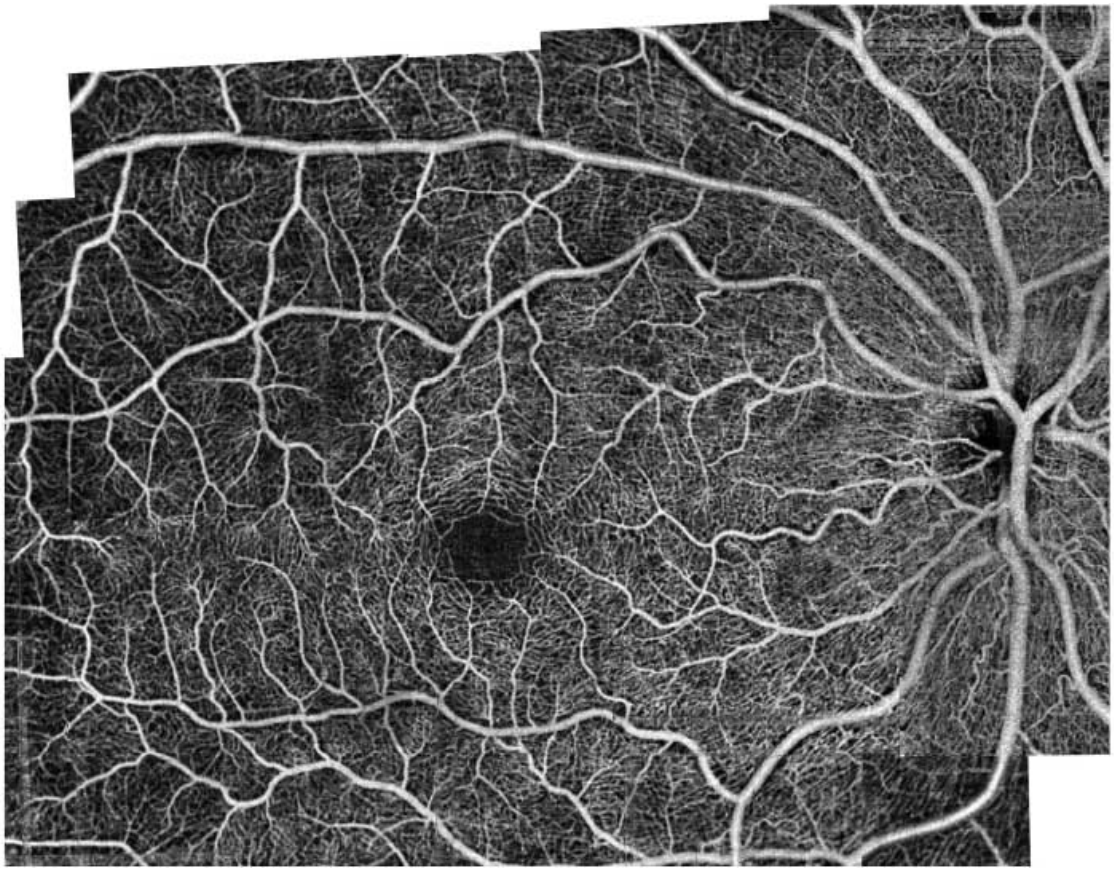

Figure 2. OCT angiography

3. Trial objectives and Design

In this observational study, we aim to evaluate whether changes in the retinal and choroidal circulation, as assessed by OCT are correlated with the degree and subtype of dementia and with the presence or absence of a positive amyloid scan.

For this purpose, patients with established AD and LBD, as well as amyloid positive and amyloid negative MCI and aged matched cognitively intact patients will be included in this cross-sectional study.

4. Selection and withdrawal of subjects

4.1 Inclusion criteria

- Cognitively intact healthy controls will be recruited from an ongoing community-recruited longitudinal cohort of cognitively intact older adults (55-85 years, S51125) who all have undergone amyloid PET at the baseline visit in the context of study S51125. Half of the subjects will be amyloid-positive and half will be amyloid-negative. In the context of study S51125 these subjects receive two-yearly neuropsychological assessment.

- MCI patients (Petersen et al., 2004 criteria) will be recruited from an ongoing memory-clinic recruited longitudinal cohort of patients with amnestic mild cognitive impairment who participate in study S55892. All subjects have undergone an amyloid PET at the baseline study in the context of study S55892. Half of the subjects will be amyloid-positive and half will be amyloid negative.

- Clinically probable AD subjects (NINCDS-AIREN criteria) will be recruited from the memory clinic UZ Leuven (MMSE 12-28). Subjects will be recruited only if they are capable of providing written informed consent.

-Clinically probable LBD (McKeith et al. criteria, 2005) will be recruited from the memory clinic UZ Leuven (MMSE 12-28). Subjects will be recruited only if they are capable of providing written informed consent.

- Capable and willing to participate

4.2 Exclusion criteria

- Personal medical history of retinal neovascularization
- Unable or unwilling to give consent

4.3 Expected duration of trial

10 minutes per person

5. Trial Procedures

1. Informed consent: AD en LDB patients will be accompanied by a personal study partner who will verify and sign whether the purpose, course and voluntary nature of the trial has been explained to the patient in a clear and understandable language, prior to signing the informed consent.

2. Medical questionnaire assessing personal medical history of cardiovascular diseases and cardiovascular risk factors. When necessary, the Electronic Health Record as well as treating physicians might be consulted to complete the questionnaire.
3. Basic non-invasive ophthalmic examination: visual acuity, slit lamp assessment of the anterior and posterior segments, lens grading and non-dilated fundus photography
4. OCT: Macula centered cube followed by optic disc centered cube, for both eyes
   Each scan takes approximately 2.5 seconds.
5. Retinal and choroidal thickness and motion decorrelation will be measured using the provided software.
6. The diagnostic performance of these OCT parameters to classify between amyloid positive vs amyloid negative controls, amyloid-positive vs amyloid negative MCI, AD and DLBD will be evaluated.

6. Assessment of efficacy

/

7. Assessment of Safety

The power and frequency of the light source used by the fundus camera and by the spectral-domain OCT are completely harmless for the human retina and cause no subjective discomfort. The OCT device uses a faint light at the near-infrared spectrum that can barely be perceived by the human eye. Pupillary dilatation is not required.

8. Statistics

8.1 Sample size

As of now, there is no data available on the distribution of flow index or vessel density in the population. This exploratory study is aimed to provide data on the distribution of these parameters in the healthy and diseased population. For this purpose, we will recruit 15 amyloid-positive and 15 amyloid-negative cognitively intact controls, 15 amyloid-positive and 15 amyloid-negative MCI, 15 clinically probable AD in an early stage and 10 clinically probable LBD.

8.2 Analysis

Demographics and measured parameters will be analyzed with descriptive statistics (mean ± standard deviation). Image analysis for the OCT will be performed with the software provided by the manufacturer. To evaluate the diagnostic performance of these parameters in distinguishing between subcategories, 'receiver operating characteristic' (ROC) curves with 'area under the curve' (AUC) analysis will be used. Logistic regression models will be used to assess the association between retinal/choroidal vascular parameters and cardiovascular risk factors. Statistical significance will be based on two-sided P-values of <0.05. All statistical analyses will be performed using SPSS 20.0 for Mac (SPSS Inc., Chicago, IL, USA).

9. Quality assurance

To assure maximal quality and reproducibility, the trial protocol will be followed rigorously.

10. Direct access to source data and documents

Demographics and disease-related parameters (functional assessment, biochemistry and imaging) will be retrieved from the electronic medical health record. When not available, additional tests will not be performed.

11. Ethics and regulatory approvals

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (2008), the principles of GCP and in accordance with all applicable regulatory requirements. This protocol and related documents will be submitted for review to Ethics Committee of the University Hospitals Leuven.

The Study will be conducted only on the basis of prior informed consent by the Subjects to participate in the Study. We shall obtain a signed informed consent form (ICF) for all patients prior to their enrollment and participation in the Study in compliance with all applicable laws,

regulations and the approval of the (local) Ethics Committee, if required. We shall retain such ICFs in accordance with the requirements of all applicable regulatory agencies and laws.

12. Data Handling

We shall treat all information and data as confidential and shall not disclose such information to any third parties or use such information for any purpose other than the performance of the Study. The collection, processing and disclosure of personal data, will comply with applicable personal data protection and the processing of personal data (Directive 95/46/EC and Belgian law of December 8, 1992 on the Protection of the Privacy in relation to the Processing of Personal Data). We will protect the data from disclosure outside the research according to the terms of the research protocol and the informed consent document. The subject's name or other identifiers will be stored separately from their research data and replaced with a unique code to create a new identity for the subject.

13. Data Management

Volunteers will be matched to an anonymous identifier. Data will be recorded electronically in a spreadsheet. Images will be exported and permanently removed from the diagnostic device.

14. Translational research

No biological material will be collected/shipped/stored/used for the study

15. Publication Policy

Any publication will be submitted to all co-authors and sponsors for review at least thirty (30) days prior to submission or disclosure. Sponsor shall have the right to delay the projected publication for a

period of up to three (3) months from the date of first submission to the Sponsor in order to enable the Sponsor to take steps to protect its intellectual property rights and know-how.

16. Insurance/Indemnity

In accordance with the Belgian Law relating to experiments on human persons dated May 7, 2004, Sponsor shall assume, even without fault, the responsibility of any damages incurred by a Study Patient and linked directly or indirectly to the participation to the Study, and shall provide compensation therefore through its insurance.

17. Financial Aspects

Volunteers will not be charged with the cost of the additional examinations.

No commercial interests to declare.

18. References

1. Patton, Niall, et al. "Retinal vascular image analysis as a potential screening tool for cerebrovascular disease: a rationale based on homology between cerebral and retinal microvasculatures." *Journal of anatomy* 206.4 (2005): 319-348.
2. Cheung, Carol Yim-lui, et al. "Microvascular network alterations in the retina of patients with Alzheimer's disease." *Alzheimer's & Dementia* 10.2 (2014): 135-142.
3. Huang, David, et al. "Optical coherence tomography." *Science* 254.5035 (1991): 1178-1181.
4. Spaide, Richard F., James G. Fujimoto, and Nadia K. Waheed. "Optical Coherence Tomography Angiography." *Retina* 35.11 (2015): 2161-2162.