# Progression of brain lesions in migraine. The Population-Based CAMERA MRI follow-up study

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In the present study we want to demonstrate progression of brain lesions and associated impairment of brain function in migraineurs vs. non-migraine controls. To this extent we have the following objectives:1) Measure progression of brain lesions of...

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Headaches |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON30636

**Source**
ToetsingOnline

**Brief title**
Brain lesions in migraine

### Condition

- Headaches

**Synonym**
migraine

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum
**Source(s) of monetary or material Support:** Ministerie van OC&W,Combinatie geldstromen o.b.v. NWO VICI subsidie (prof. Ferrari;LUMC);en aangevraagde subsidie

(Nederlands Hartstichting;waardoor ook het uitgangsonderzoek in 1999/2000 werd gesubsidieerd; thans bevindt deze aanvraag zich in de hoor-/wederhoor fase. Tevens is een subsidie aangevraagd bij de "National Institutes of Health" (VS) t.b.v. deze studie.

## Intervention

**Keyword:** cerebral infarction, cerebral ischemia, cerebrovascular disorders, magnetic resonance imaging

## Outcome measures

### Primary outcome

Differences in descriptive statistics between the migraine cases and controls will be examined with *2 test, unpaired t tests, and one-way analyses of variance. Volume of white matter lesions and number of infarcts will be analyzed cross-sectionally as well as longitudinally. Cross-sectional analyses will concentrate on prevalence of participants with a high WML load (similar criteria as to CAMERA 1) and on the number of (posterior circulation) infarcts prevalent. The same methods will be used as was reported for CAMERA 1. Longitudinal analyses will concentrate on progression of lesions (=primary endpoint): either increase in number and/or total volume of WMLs, and/or increase in size of existing infarcts and/or the presence of new infarcts together. Progression of brain lesions over a period of 6 years in relation to migraine diagnosis and characteristics will be tested using multivariate models, in which will be controlled for relevant confounding factors. This follow-up data will be analyzed using both logistic regression, as well as regression based on a Cox proportional hazard model. Confounders will be entered into final models. Analyses of the PFO measurements will be categorical. Multi-variate logistic regression, adjusting for confounders will

be to analyze the association of PFO to migraine diagnose, MRI-characteristics, and combined. All parameters of the BST are continuous, and will be analyzed in relation to migraine status and presence of cerebellar lesions. Results of the cognitive testing will be analyzed cross-sectional as well as longitudinal, also in relationship to migraine characteristics and/or brain lesions. For both the cerebellar function tests and the cognitive outcomes, the analyses will be based on linear regression, after ascertaining the normality of their distribution.

Statistical analyses and appropriate regression diagnostics will be conducted with current SPSS statistical software (SPSS Inc, Chicago, Ill). In this study, if we assume 100 controls and 100 cases of migraine with aura, and that 15% of controls will have an indication of lesion progression, we have 90% power (alpha 5%) to detect a significant risk ratio of 2.0.

**Secondary outcome**

nvt

# Study description

**Background summary**

Background:
Migraine is a highly disabling, multifactorial, episodic, neurovascular brain disorder, affecting 12% of the general population and associated with a 3-7 fold increased risk of cerebral and myocardial infarction. In 2000 we scanned 295 migraineurs and 140 healthy subjects randomly identified from the general population with MRI and found an increased risk of cerebellar infarcts and cerebral, cerebellar and pontine white matter hyperintensities in migraineurs (Dutch CAMERA study: Kruit MC et al; JAMA 2004, Brain 2005, Stroke 2006; NHS

grant 97-108). The risk was greatest in those with aura and higher with increasing attack frequency, suggesting a causal relationship. Possible mechanisms for the brain abnormalities include:
i) repeated cerebral hypoperfusion during attacks (accompanying cortical spreading depression, the underlying mechanism for migraine aura); and
ii) paradoxical cerebral emboli due to the high prevalence (up to 60% of patent foramen ovale (PFO) in migraineurs. Functional studies in clinic-based migraineurs have shown sub-clinical cerebellar dysfunction (Sandor P, et al. Annals Neurol
2001) and increased recruitment of brain areas when executing motor tasks (Rocca MA, et al. Stroke 2003), suggesting impaired brain function in severe migraineurs. To establish if repeated migraine attacks may indeed affect brain structure and function, an unbiased, population-based, longitudinal study is needed, assessing, within the same cohort, the presence, change and severity of:
- migraine characteristics;
- MRI brain lesions; and
- brain function.
Positive answers to these questions would call for an earlier and more agressive prevention of migraine attacks
and associated brain damage.
We propose to:
- rescan the original CAMERA cohort with MRI
- compare the results with the scans from 2000; and
- correlate the findings with results from (follow-up) tests for migraine characteristics, cardiovascular risk factors,
brain function, and (now newly assessed) presence of PFO.

Hypothesis:
We hypothesize that repeated migraine attacks are associated with progressive brain damage and impaired brain function as a result of recurrent cerebral ischemia during recurrent migraine attacks. We predict that migraine patients, in particular those with aura and high attack frequency, will show an increase in brain lesion load and impaired brain function when compared to controls and with examinations done seven years ago in the CAMERA I study.

**Study objective**

In the present study we want to demonstrate progression of brain lesions and associated impairment of brain function in migraineurs vs. non-migraine controls.

To this extent we have the following objectives:

1) Measure progression of brain lesions of over time in migraine patients and control subjects over a period of seven years;
2) Establish a correlation between changes in brain lesion load and specific

migraine characteristics (in particular migraine aura, attack frequency, use of migraine medication) and presence of PFO;
3) Test for impaired cerebellar and cognitive function, and correlate findings with MRI abnormalities and migraine characteristics.

Divided into categories:

A Evaluation of progression in brain lesions
•Rescanning of CAMERA 1 study population (n=435) using the same MRI systems to measure progression over time;
•Assessing progression of the lesion load- either by identifying an increase of the lesion load within already affected patients, or by identifying newly affected patients;

B Evaluation of contribution of other factors in the cause of lesions in migraineurs
•Correlating migraine characteristics to difference in lesion load.
•Evaluating the presence of a PFO by means of transcranial Doppler (TCD) and correlating these data to white matter hyperintensities and infarcts.

C Evaluation of functional consequences
•Test for impaired cerebellar function with a set of non-invasive tests and correlate findings with MRI abnormalities;
•Test for cognitive function with a cognitive test battery similar to CAMERA 1; results will be compared with baseline test results.

Final aim is - with answers to these questions - to answer the important healthcare issue whether migraine should be treated more aggressively and/or earlier with preventative agents in order to prevent migraine attack-related brain damage.

**Study design**

CAMERA 2 will be a population-based, longitudinal follow-up study. Participants of the CAMERA 1 study (n=435) will be re-invited for the proposed follow-up study. Only previous participants who are still willing and able to give informed consent will be included (CAMERA 1 inclusion criteria: adults age 30-60 years, signed informed consent, participants of MORGEN-study). In 2000 all participants gave permission to be re-invited for follow-up research. Subjects with contra-indications for MRI will be excluded. We estimate to include at least 200 migraine cases and 100 controls.

All participants will undergo the same examinations as was previously performed including structured telephone interview, MR imaging of the brain, standard neurological exam, and cognitive testing. This effectively implies a 7 year

follow-up of the same population (longitudinal population-based case-control study). We will add to this set of measures transcranial doppler (TCD) and a body sway test (BST). These examinations pose no or minimal risk. All examinations will be done with the same methods and precautions used in a standard medical examination, and are supervised by a physician.

In more detail, all participants will undergo:
- a telephone interview, with questions about general health condition, present and/or past diseases and brain disease risk factors, and (cases) additional questions about their migraine, focussing on differences compared to 2000. We will check whether the controls have had migraine attacks in the past 7 years. A detailed history of migraine characteristics, in particularly aura and attack frequency, will be recorded.
- re-scanning of the brain using the same 1.5T MRI scanner in Maastricht (ACS-NT; Philips Medical Systems, Best, The Netherlands) and the same 1.0T MRI scanner in Doetinchem (Magnetom Harmony; Siemens AG, Erlangen, Germany).
- TCD, to be performed in collaboration with Prof. dr. W.H. Mess (neurophysiology, AZM, Maastricht), who is an expert in this field, to assess whether a PFO is present.
- cognitive testing, to be administered by a trained medical students, in cooperation with Prof.dr. H. Middelkoop (clinical neuropsychology, LUMC, Leiden). The same test battery as in CAMERA 1 will be used (15 word memory test, stroop test, word fluency, letter digit substitution test, peg-board test, depression scale and MMSE). Long and short term memory, concept shifting, psychomotor speed, organization, visuo-spatial ability, motor speed, and characteristics of depressive disorder can be characterized by the results of these tests.
- Cerebellar function tests, in collaboration with prof.dr. C. de Zeeuw (Neuroscience Institute, EMC Rotterdam) and dr. B. Bloem (Medical director, Parkinson Center Nijmegen) to measure several cerebellar functions with non-invasive tests and compare these data between migraineurs and non-migraineurs. The results of these tests inform us about cerebellar functioning and the possible influence on it by damage from cerebellar (ischemic) lesions.

WML-load quantification
An automated image processing method that was recently developed and validated at the McConnell Brain Imaging Center of the Montreal Neurological Institute (MNI) under the direction of Dr Alex Zijdenbos for the Age, Gene/Environment Susceptibility (AGES) study, a collaborative population study conducted by the National Institute on Aging and the Icelandic Heart Association, will be used to segment and quantify WML at baseline and follow up to obtain quantitative data on volume changes of these lesions over time. The elimination of intra- and inter-rater variability by automatic analysis enables the system to detect small changes over time, which are not readily detectable through conventional analysis techniques. The WML quantification is part of a fully automatic validated "pipeline" image analysis framework, which has been successfully

applied it to a number of large-scale, multicenter studies (>1,000 MRI scans). This pipeline system is based on robust and sophisticated image processing algorithms.

Infarct rating
Infarcts will be scored visually, in a qualitative fashion by experienced readers, because reliable automated methods to automatically segment infarcts are not available. Baseline scans and follow up scans will be projected next to each other on a 30 inch screen. Using longitudinal registration and resampling, corresponding slices will be linked. The software for handling, hanging and viewing of the images has also been developed for the AGES study. The presence of infarcts will first be assessed on the follow-up scan. Each detected infarct will be traced back on the baseline scan, and based on the comparison of the two scans an assessment will be made for each infarct whether it was already present on the previous scan, and if so whether it increased in size (measurement of largest diameter of the infarct in the axial plane) or whether it remained stable. To avoid any type of bias, two experienced readers will independently read all MRI images. Before start of the actual rating, readers will score each 50 selected sets (of baseline and new) MRI examinations for training purposes; training results will be discussed to steepen learning curve. During the actual rating, readers are unaware of clinical data. In case of discrepancies between two readers, a consensus will be reached after discussion between the two readers. The intra-rater reliability will be estimated by having 25 pairs of randomly selected scans cycle through the total sample of scans in a random order so the readers do not know they have already read the scans.
Infarcts are defined as non-mass parenchymal defects, with a vascular distribution, isointense to CSF-signal on all sequences, and, when supratentorial, surrounded by a hyperintense rim on FLAIR and PD images. Number, location, vascular territory and size of infarcts will be recorded, including data on increase/decrease in size of existing infarcts and/or presence of new infarcts. Virchow-Robin spaces will be excluded as infarcts, based on location, shape, size and absence of a hyperintense border.

## Study burden and risks

All potential participants will be contacted by the study coordinator two weeks after recieving the invitation. They will be asked to particpate and can ask questions about the study participantion before deciding to participate. After signing the informed consent form, an appointment will be made for an interview by telephone which will take about 20 minutes.

1-3 Weeks after this phonecall the participants will visit the research centre once. This visit will take a maximum of 3 hours and includes above mentioned investigations which are all harmless.

# Contacts

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**Scientific**
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# Trial sites

## Listed location countries

Netherlands

# Eligibility criteria

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

## Inclusion criteria

Participants in CAMERA I MRI study
Males and females
Age between 40 and 70 yrs
Signed informed consent in 1999-2000
Cases: Diagnosed with migraine
Controls: Screened negative

## Exclusion criteria

Will-unabled
MRI contra indicated

Claustrophobia
Unable to sign informed consent

# 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: | Pending |
| Start date (anticipated): | 01-09-2007 |
| Enrollment: | 300 |
| Type: | Anticipated |

# Ethics review

Approved WMO

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|---|---|
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

# 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 | NL12850.058.07 |