

Chronification and reversibility of migraine.

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We want to unravel the role of depression and OAHM in the chronification of migraine, assess the (permanent and reversible) short- and long-term consequences of chronic migraine and OAHM on the brain, and decipher some of the underlying...

Ethische beoordeling	Positief advies
Status	Werving gestopt
Type aandoening	-
Onderzoekstype	Interventie onderzoek

Samenvatting

ID

NL-OMON22952

Bron

NTR

Verkorte titel

CHARM

Aandoening

(chronic) migraine, migraine, medication-overuse headache

Ondersteuning

Primaire sponsor: Leiden university Medical Center

Overige ondersteuning: NWO VIDI grant

Onderzoeksproduct en/of interventie

Uitkomstmaten

Primaire uitkomstmaten

The primary outcome measure is the relative reduction in headache days per month, in a comparison of the last month of withdrawal (month 3) with the baseline period (month -1). A

headache day is defined as a day on which there is at least one period of \geq 4 hours of continuous headache. The relative reduction will be measured in the Btx and placebo groups and will be adjusted using multivariate analysis for depression scores at baseline and support by the headache nurse. As an alternative primary outcome measure, we will measure quality of life during the withdrawal trial. This will be measured by the Sumscore on the SF-36 questionnaire at timepoint 0, 1, 2 and 3.

Addendum: The primary outcome measure is the relative reduction in headache days per month, in a comparison of the last month of withdrawal (month 3) with the baseline period (month -1). A headache day is defined as a day on which there is migraine or non-migraine headache. The relative reduction will be measured in the Btx and placebo groups and will be adjusted using multivariate analysis for depression, anxiety, gender, age, headache days at baseline and support by the headache nurse.

Toelichting onderzoek

Achtergrond van het onderzoek

In this study we will perform a randomized, double blind, placebo-controlled trial in which chronic migraine patients (n=180) with medication overuse (OAHM) will be randomized to withdrawal therapy with accessory Botulinum toxin A (Btx) injections or with placebo-treatment, and minimal or maximal support of a headache nurse.

We will perform an MRI-study in the first 100 chronic migraineurs included, before and after withdrawal of medication. MRI will also be performed in matched control groups, consisting of patients with episodic migraine, patients with chronic pain, patients with a depressive disorder and healthy controls (n=20 for each control group) to correct for any bias by migraine specific, chronic pain related- or affective changes. Magnetic resonance imaging will be performed at baseline in all chronic migraineurs and control groups. The imaging protocol will be repeated in chronic migraineurs after completion of the withdrawal phase (at three months) and at one year after start of withdrawal to study short- and long term changes in that specific group. Blink reflexes (as a marker of excitability of the trigeminovascular system) will be tested at baseline in both the chronic migraine patients, and at 3 and 12 months in the chronic migraine patients. At the same time points as the blink reflex (ETVS) and MRI-scans, questionnaires will be taken and blood samples will be drawn.

Doel van het onderzoek

We want to unravel the role of depression and OAHM in the chronification of migraine, assess the (permanent and reversible) short- and long-term consequences of chronic migraine and OAHM on the brain, and decipher some of the underlying neurobiological mechanisms.

We hypothesize for the withdrawal phase, that:

1. Treatment with Botulinum toxin A (Btx) injections (at the start of the therapy) will increase the success rate of withdrawal therapy or will improve quality of life during the withdrawal period:

A. The presence of comorbid depressive symptoms is associated with a reduced success rate of withdrawal of OAHM in patients with chronic migraine;

B. The support of a headache nurse during the withdrawal period will increase the success rate of withdrawal therapy;

C. Presence of comorbid depressive symptoms, baseline migraine characteristics (e.g. attack frequency, duration of attacks, number of medication days per month) and baseline brain structure and function (BSF) and excitability of the trigeminovascular system (ETVS) measures are predictors of the success rate of withdrawal therapy.

We hypothesize for the baseline imaging phase, that:

2. Before treatment, changes in (regional) BSF and ETVS can be identified in chronic migraineurs with medication overuse. The use of different control groups (episodic migraineurs, depressive patients, chronic pain patients and healthy controls) will allow to differentiate changes in (specific) structures or functions associated with chronification of migraine from changes associated with depression and/or chronic pain.

We hypothesize for the longitudinal imaging phase, that:

3. After withdrawal, changes in BSF and ETVS compared to baseline will point towards transmutable structures or functions involved in and/or predisposing to chronification of migraine:

A. Changes in BSF and ETVS after withdrawal therapy will depend on a) accompaniment of Btx injections and;

B. The presence of depressive symptoms;

C. Specific MRI markers of BSF correlate with measures of ETVS.

Onderzoeksopzet

-1 month, 0, months 3, 6, 9, 12.

Addendum: The difference between maximal versus minimal support by a headache nurse, and depressive (HADS \geq 8) versus non-depressive chronic migraineurs will be assessed by measuring the absolute and relative reduction in migraine and headache days on time points 3, 6, 9 and 12, the number of patients achieving a 50% or more decrease from baseline (month -1) in the frequency of migraine days and migraine episodes at both time points and

absolute and relative reductions of HIT-6, SF-36 CES-D and HADS-D scores at time points 3, 6, 9 and 12. The differences in baseline characteristics (i.e. headache characteristics, accompanying symptoms, depression, anxiety) between responders ($\geq 50\%$ reduction in headache days) versus non-responders will be examined.

Headache and medication overuse relapse rates at $t=12$ will be assessed and compared between Btx and placebo-treatment, minimal or maximal support by the headache nurse and depressive versus non-depressive groups. The change in reactivity of the trigeminal blink reflex during the course of the trial will be assessed. Blink reflex will be tested at time points 0, 3 and 12.

Onderzoeksproduct en/of interventie

Participants will be randomized to receive either:

1. "Verum": Withdrawal therapy with one-time concomitant botulinum toxin A injections in 31 locations according to the injection protocol by Allergan (total 155U);
2. "Placebo": Withdrawal therapy with one-time concomitant low-dose botulinum toxin A injections in the facial region and NaCl injections in the other regions according to the injection protocol by Allergan (Total 17.5U).

Withdrawal therapy is considered standard treatment for this patientgroup and takes three months. During this time, patients will be guided by a trained headache-nurse.

At the end of the three-month withdrawal period, primary outcomes will be assessed. All participants who have successfully completed the withdrawal period, but are still suffering from chronic migraines will be offered single treatment (open-label) with botulinum toxin A. This group will consist of participants from both the verum and placebo groups, but due to blinding, initial treatment is not known at this point).

Contactpersonen

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Wetenschappelijk

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Deelname eisen

Belangrijkste voorwaarden om deel te mogen nemen (Inclusiecriteria)

Suffering from chronic migraine according to the ICHD-II criteria for chronic migraine with medication overuse according to the ICHD-II criteria.

Belangrijkste redenen om niet deel te kunnen nemen (Exclusiecriteria)

1. General exclusion criteria:

A. Age under 18 years;

B. Other neurological conditions that may in the opinion of the investigators may interfere with the trial. Any oncological or psychiatric disease, other than the specific types described in the inclusion criteria;

C. Any cognitive disorders and/or behavioural problems which in the opinion of the clinician may interfere with the study;

D. Current abuse of soft drugs or hard drugs or history of abuse of soft drugs or hard drugs in the past 12 months as defined in the DSM-IV criteria under 'Substance abuse' or 'Substance dependence'.(abuse of amphetamines, cocaine, heroin, cannabis);

E. Use of non-triptan or non-analgesic acute anti-headache medication (e.g. ergots, opioids, barbiturates);

F. Pregnancy, planned pregnancy, current nursing. Additionally, all participants will be required to use adequate contraceptive methods;

- G. Inability to complete the (electronic) diary in a sensible and accurate manner;
- H. Enrolment in other studies that in the opinion of the clinician may confound the results of this study.

2. Btx-specific exclusion criteria:

- A. Any motor neuron disorder;
- B. Hypersensitivity to any botulinum toxin preparation or to any of the components in the formulation;
- C. Infection at the proposed injection site(s);
- D. (Suspected) clotting disorder; either of pathological or iatrogenic origin (e.g. caused by marcoumar, sintrom).

3. MRI-specific exclusion criteria:

- A. Implanted pacemaker or implanted defibrillator-device;
- B. Surgical clips in cerebral vasculature;
- C. Metal debris in the eyes;
- D. Non-removable hearing-aid;
- E. Non-removable neurostimulator;
- F. Hydrocephalus-pump;
- G. Denture with magnetic fixation;
- H. Copper containing Intra-uterine Device;
- I. History of surgery in which metal implants were implanted;
- J. Weight over 160kg.

Onderzoeksopzet

Opzet

Type:	Interventie onderzoek
Onderzoeksmodel:	Parallel
Toewijzing:	Gerandomiseerd
Blinding:	Dubbelblind
Controle:	Geneesmiddel

Deelname

Nederland	
Status:	Werving gestopt
(Verwachte) startdatum:	01-09-2012
Aantal proefpersonen:	180
Type:	Werkelijke startdatum

Voornemen beschikbaar stellen Individuele Patiënten Data (IPD)

Wordt de data na het onderzoek gedeeld: Nog niet bepaald

Ethische beoordeling

Positief advies	
Datum:	15-05-2012
Soort:	Eerste indiening

Registraties

Opgevolgd door onderstaande (mogelijk meer actuele) registratie

Geen registraties gevonden.

Andere (mogelijk minder actuele) registraties in dit register

Geen registraties gevonden.

In overige registers

Register	ID
NTR-new	NL3294
NTR-old	NTR3440
Ander register	EudraCT : 2011-005124-18
ISRCTN	ISRCTN wordt niet meer aangevraagd.

Resultaten

Samenvatting resultaten

<https://academic.oup.com/brain/article/142/5/1203/5457721>