Next generation phenotyping in essential tremor

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Primary Objective: To determine different familial features (demographical, clinical, neurophysiological) in essential tremor families and subsequently clustering these features into subtypes of familial essential tremor. Secondary Objective(s): To...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Movement disorders (incl parkinsonism)
Study type	Observational invasive

Summary

ID

NL-OMON49466

Source
ToetsingOnline

Brief title
NG-PIET

Condition

- Movement disorders (incl parkinsonism)

Synonym
essential tremor, tremor

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Tremor

Outcome measures

Primary outcome

In this study we will try to identify a familial phenotype of essential tremor in our population, based on clusters of the discovered familial features. Based on our recently published review (4) we will address the following features of interest: age at onset, cranial tremor, dystonia, alcohol responsivity and tremor frequency.

Secondary outcome

Features of secondary interest are:

- Disease progression

- Cerebellar signs (intention tremor via finger-to-nose manoeuvres, via finger-to-finger manoeuvres, tandem gait difficulty)

- Parkinsonism (bradykinesia, rigidity)

- Tremor severity (Fahn-Tolosa-Marin Essential Tremor Rating Scale part A and B, visual analogue scale)

- Neurophysiological features (frequency variability, coherence analysis)

- Discrepancies between self-reported and test-based alcohol responsivity

Study description

Background summary

Tremor is defined as an involuntary, rhythmic, oscillatory movement of a body part. Essential tremor is the most common movement disorder in adults (1), and

is considered to be a highly heritable disorder. Estimates for the proportion of essential tremor patients with a positive family history range from 20% to 90%. It is largely unknown, however, to what extend family members share overlapping features like demographical (e.g. age at onset), clinical (e.g. tremor/body distribution) and neurophysiological (e.g. tremor frequency) characteristics.

Knowledge about familial aggregation of essential tremor features is relevant for patient counseling. Clinicians often care for patients who have several affected family members, as well as younger, at-risk relatives, most importantly children and grandchildren. For these patients, it would be informative to know whether the features in their family members can help predict their own disease course, as essential tremor can have a serious impact on patients* personal and professional lives.

Moreover, information on the familial aggregation of features in essential tremor would be relevant scientifically, particularly in the field of genetics. In recent years, the search for disease-related genes has intensified greatly, by means of all recent technological developments (linkage analysis, whole exome sequencing and genome-wide association studies) (2), but essential tremor genetics still awaits a breakthrough discovery that will improve the understanding of this disorder. A key issue is that the essential tremor syndrome transpires to be a family of diseases rather than a single disease entity (1). The suggested way forward is to increase focus on phenotyping and phenotype-genotype association (2): the Internal Parkinson and Movement Disorders Society*s tremor task force especially chose a classification scheme that promotes detailed phenotyping in their 2018 Consensus Statement (3), to facilitate the discovery of specific (genetic) etiologies.

We have recently written a review in which the evidence in the literature for familial aggregation of various features in essential tremor is evaluated, and we established that alcohol responsivity and neurophysiological features have been studied poorly or not at all (4).
It is a well-known fact that approximately half the patients with essential tremor report a positive effect of alcohol on their tremor. In the only available study (5), responsiveness was either consistently present or absent in 80% of the families, while in 20% the self-reported effect of alcohol was heterogenic. Familial aggregation was made likely, but only descriptive statistics were employed. Moreover, only self-reported alcohol responsivity was assessed, while the correlation between self-reported and actual responsivity (assessed with a validated test (6)) is known to be limited (7). Based on the study described above, it is our hypothesis that alcohol responsivity runs in essential tremor families.
Clinical neurophysiological tests can help a neurologist to establish a diagnosis. Polymyography (poly-EMG), combined with accelerometry, registers the tremor frequency and amplitude in different postures, movements and during the performance of different tasks. Polymyography can objectify tremor

characteristics (e.g. frequency, frequency variability, etc.), making it a valuable tool for tremor differentiation (8). Whether neurophysiological features aggregate in essential tremor families has never been studied, but may be helpful in defining familial phenotypes, which may ultimately prove useful to establish genotypes.

Next, we will try to establish a familial essential tremor phenotype-subtype within our population, based on clustering of heritable/familial disease features including alcohol responsivity and neurophysiological features. This information can be incorporated in our project Next Generation Sequencing in Movement Disorders (METC-2014/119), in which patients with heritable essential tremor are investigated genetically.
This extensive phenotyping can be used to capture the phenotype in essential tremor families precisely. Ultimately, this will clear the path for phenotype-genotype association and the discoveries of new genes.

Study objective

Primary Objective:
To determine different familial features (demographical, clinical, neurophysiological) in essential tremor families and subsequently clustering these features into subtypes of familial essential tremor.

Secondary Objective(s):
To establish whether neurophysiological features run in essential tremor families.
To establish whether alcohol responsivity is a familial feature in essential tremor.

Study design

This is a cross-sectional study that consists of two parts: an observation and an intervention part. In part A, participants are assessed clinically (using history taking and neurological examination) and neurophysiologically (using EMG, accelerometry and video-recording). In part B, participants perform a validated test for alcohol responsivity. Both of these parts are relevant to phenotyping of the patients.
Part A is performed during a single visit to the UMCG, or to a rented external location. Both parts have a duration of 1-2 hours. The duration of the study is equal to the duration of the inclusion of patients, as there is no follow-up.
We aim to include the required number of subjects within 3 years.

Study burden and risks

Nature and extent of the burden and risks associated with participation, benefit and group relatedness: There are no issues of concern applicable for

the individual patient. Regarding part A of this study, the potential risk for the subjects is considered to be negligible because no invasive apparatuses are used and the tasks that are included in the study are not burdensome. A one-time visit to the UMCG has to be made, or to an external location rented by the UMCG. There an interview, extensive neurological exam and a poly-EMG will be conducted.
Participants of part B of this study, where alcohol responsivity in essential tremor families is studied, takes place at the UMCG (or externally rented location) as well. The investigator will assess whether the patient is suitable to participate, based on a questionnaire. The risk associated with participation in this part of the study is considered minimal, because the reached blood alcohol concentration is low (0.6%), the majority of participants will have experience with drinking this amount of alcohol, and because safety instructions are in place. The burden can be considered as acceptable, it is possible that participants experience a short-term rebound effect of their tremor the morning after the alcohol intake.

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

- For the index patient: diagnosis of essential tremor syndrome by neurologist, in line with the consensus statement put forward by the Tremor Investigation Group of the Movement Disorders Society and a minimum age of 18 years.
- For the family: a minimum of 3 affected relatives, belonging to a minimum of 2 generations, willing to participate.

Exclusion criteria

- Part A, if the patient has a silver allergy
- Part A, if the patient has a pacemaker
- Part B, if the patients alcohol history is indicative of (previous) alcohol abuse
- Part B, if the patient is pregnant or breastfeeding
- Part B, if the patient uses medication which is contraindicated in combination with alcohol

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Other

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	12-10-2020
Enrollment:	100
Type:	Actual

Ethics review

Approved WMO Date:	23-03-2020
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-01-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL72350.042.19