Brain Vascular Malformations Research Network: Predictors of Phenotype and Clinical Course. Project 3: Cerebral Hemorrhage Risk in Hereditary Hemorrhagic Telangiectasia

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Objective and Research QuestionsTo identify predictors of brain outcomes in HHT patients, we propose to leverage our multicenter network of HHT Centers to characterize comprehensive brain outcomes.Study Aims:Aim 1: We hypothesize that the presence...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Cardiac and vascular disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON50567

Source
ToetsingOnline

Brief title
BVMC3-6203

Condition

- Cardiac and vascular disorders congenital
- Central nervous system vascular disorders
- Vascular haemorrhagic disorders

Synonym
cerebral-arteriovenous-malformation hereditary-hemorrhagic-telangiectasia

Research involving

Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: National Institutes of Health (NIH);National institute of neurological desorders and stroke (NINDS)

Intervention

Keyword: brain arterioveneus malformation, cerebral arteriovenous malformation, Hereditary-hemorrhagic-telangiectasia, Rendu-Osler-Weber disease

Outcome measures

Primary outcome

To identify predictors of brain outcomes in HHT patients. We propose to leverage our multicenter network of HHT Centers to characterize comprehensive brain outcomes. We hypothesize that the presence of BAVMs (vs. HHT patients without BAVMs) and multiplicity of BAVMs will be associated with worsening functional outcome. We will use the modified Rankin Score (mRS) to measure the functional outcome.

Furthermore to define a severe bleeding phenotype in HHT for clinical trial readiness. We hypothesize that weekly nasal bleeding duration (Patient-Reported Outcome Cumulative nasal Bleeding duration, or PRO-CB) in HHT will predict the need for invasive or life-sustaining therapies (surgery, urgent packing, blood transfusions, iron infusions). We propose to measure PRO-CB longitudinally in HHT patients and correlate with the need for invasive or life-sustaining therapies (primary outcome), as well as with ICH risk from BAVMs and with bleeding in other HHT organ phenotypes (including pulmonary AVMs and GI telangiectasia).

Secondary outcome

To identify genetic predictors and circulating biomarkers of severe bleeding and brain outcomes in HHT. We hypothesize that there are shared predictors of severe bleeding from the nose and brain in HHT patients, and that identifying these predictors will allow for selection of *at-risk* patients for clinical trials. Specifically, we will evaluate potential genetic, plasma protein biomarker and circulating miRNA biomarker predictors of PRO-CB. Markers associated with PRO-CB will then be tested for association with ICH, and with other brain outcomes and HHT severity phenotypes.

Study description

Background summary

Heriditary hemorrhagic telagiectasia (HHT) is a condition characterized by blood vessel malformations, called telangiectasia and arteriovenous malformations (AVMs), occurring in the brain, nose, lungs, stomach, bowels and liver. Brain AVMs (BAVMs) in HHT are difficult to study because they are rare, affecting approximately 10% of people with HHT. While other types of BAVMs have been studied in depth, studies in the HHT population have been very small. This will be the first large-scale collaboration achieved by joining with 16 HHT Centers of Excellence to perform a large study of risk factors for bleeding from BAVMs, called intracranial hemorrhage (ICH), in HHT patients.

Study objective

Objective and Research Questions
To identify predictors of brain outcomes in HHT patients, we propose to leverage our multicenter network of HHT Centers to characterize comprehensive brain outcomes.

Study Aims:
Aim 1: We hypothesize that the presence of BAVMs (vs. HHT patients without BAVMs) and multiplicity of BAVMs will be associated with worsening functional outcome (modified Rankin Score (mRS)). We propose to further extend our cohorts and longitudinal mRS measures and correlate BAVM and BAVM phenotypes (lesion

number, lesion type, initial presentation, etc.) with longitudinal mRS (primary outcome), as well as with ICH. Furthermore, we propose to measure other neurologic outcomes in HHT (stroke, seizure, migraine, mRS etc.) across all HHT patients and in subgroups by organ phenotype (BAVM, pulmonary AVM, etc.) and HHT gene (ENG vs. ACVRL1).

Aim 2: To define a severe bleeding phenotype in HHT for clinical trial readiness. We hypothesize that weekly nasal bleeding duration (Patient-Reported Outcome Cumulative nasal Bleeding duration, or PRO-CB) in HHT will predict the need for invasive or life-sustaining therapies (surgery, urgent packing, blood transfusions, iron infusions). We propose to measure PRO-CB longitudinally in Cycle 3 HHT patients and correlate with the need for invasive or life-sustaining therapies (primary outcome), as well as with ICH risk from BAVMs and with bleeding in other HHT organ phenotypes (Pulmonary AVMs, GI telangiectasia, etc).

Aim 3: To identify genetic predictors and circulating biomarkers of severe bleeding and brain outcomes in HHT. We hypothesize that there are shared predictors of severe bleeding from the nose and brain in HHT patients and that identifying these predictors will allow for selection of *at-risk* patients for clinical trials. Specifically, we will evaluate potential genetic, plasma protein biomarker and circulating miRNA biomarker predictors of PRO-CB. Markers associated with PRO-CB will then be tested for association with ICH, and with other brain outcomes and HHT severity phenotypes.

Study design

This is an observational and multicenter study.

We will construct a relational database and web-based data collection instrument. Data will include demographics, symptomology, cerebral angioarchitecture, other organ involvement and HHT gene mutation results.

The database will be used to serve Aim 2 and Aim 3 but will also serve as a platform to foster further HHT research. The recruitment of HHT BAVM cases will be emphasized by use of a 3:1 ratio for enrolling non-BAVM to BAVM HHT cases, i.e., for each brain AVM recruited, 3 patients without a brain AVM will be recruited. When possible, these additional cases will be from patients in the same family to facilitate exploratory or future studies. This will provide the largest single sample available that will also have centralized expert neuroradiological adjudication of the brain phenotype.

Study burden and risks

During blood draw, subjects may experience some discomfort or slight pain at the site of needle entry into the vein. Small blood clot formation or bruising

may occur at the point of needle entry and there may be swelling in this area. There is a remote risk of fainting. Infection could occur at the place where the needle goes into the arm.

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

Patients with clinical and/or genetic confirmed HHT with or without BAVM

Exclusion criteria

none

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	25-09-2013
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	18-06-2013
Application type:	First submission
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	15-04-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	19-12-2014
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	18-10-2018

Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)
Approved WMO Date:	08-06-2020
Application type:	Amendment
Review commission:	MEC-U: Medical Research Ethics Committees United (Nieuwegein)

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	NL43359.100.13