Correlation between soluble FLT1 and clinical features of patients with Hereditary Hemorrhagic Telangiectasia

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To determine whether serum soluble VEGFR1 is also reduced in HHT2 patients and might be used as marker of disease severity.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON45691

Source
ToetsingOnline

Brief title
Soluble FLT1 in patients with HHT

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Vascular haemorrhagic disorders

Synonym
Hereditary Hemorrhagic Telangiectasia, Rendu-Osler-Weber syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Sint Antonius Ziekenhuis
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Hereditary Hemorrhagic Telangiectasia, Soluble FLT1, Soluble VEGFR1

Outcome measures

Primary outcome

Level of sFLT1 in correlation to symptom severity.

Secondary outcome

geen

Study description

Background summary

Hereditary haemorrhagic telangiectasia (HHT), also known as Rendu-Osler-Weber syndrome, is an autosomal dominant inherited disease affecting approximately 1:5000 people. Most cases of HHT are the result of a pathogenic DNA sequence variant in ENG (type 1), ACVLR1 (type 2) or SMAD4 gene leading to multi-systemic vascular dysplasia. Affected individuals often suffer from epistaxis and bleeding in the gastrointestinal tract due to mucosal telangiectasia, frequently leading to iron deficiency anaemia. Pulmonary (pAVM), cerebral (cAVM) and hepatic vascular malformations (hVM) can cause major morbidity and mortality. Penetrance of symptoms vary greatly between disease causing mutations, within families and with age.
Angiogenesis is tightly controlled by pro- and anti-angiogenic factors. An imbalance in this process can lead to excessive or insufficient angiogenic responses, which has been associated with different diseases including HHT. Studies in humans and animal models have demonstrated that for transforming growth factor-β (TGF-β) and VEGF signalling play crucial roles in maintaining physiological vascular homeostasis by modulating endothelial cell function. Flt1 is a receptor for vascular endothelial growth factor receptor [VEGF], whereas endoglin [ENG] is an auxiliary receptor TGF-β super-family members. Both signalling pathways modulate angiogenesis and are involved in vascular homeostasis. Increased levels of soluble Flt1 and soluble ENG dysregulate VEGF and TGF-β signalling respectively, resulting in endothelial dysfunction of maternal blood vessels.
Recently, we have investigated the mechanisms underlying vessel malformations in Acvrl1+/- mutant mice, a model of HHT2 and have found that excessive angiogenesis in HHT2 is attributed to reduced expression levels of soluble VEGFR1 (sFLT1), providing scientific evidence supporting the use of anti-VEGF

therapies in HHT. Serum soluble VEGFR1 has been suggested to be a biomarker for the development of preeclampsia, neovascular age-related macular degeneration and response to anti-angiogenic therapies. Here our aim is to determine whether serum soluble VEGFR1 is also reduced in HHT2 patients and might be used as marker of disease severity.

Study objective

To determine whether serum soluble VEGFR1 is also reduced in HHT2 patients and might be used as marker of disease severity.

Study design

Patients with HHT type 2 routinely visiting the pulmonary outpatient clinics will be informed about the study during a regular visit. Patients will be given information about the study and given 2 weeks to think about participation. After 2 weeks dr AE Hosman will contact the patient to give them additional information or answer any questions and ask them whether they want to participate. If they would like to participate patients will get an appointment following another regular check-up at the pulmonary outpatient clinics. Any questions may be answered and additional information may be given if the participant wishes so. Informed consent will be signed when participants want to participate and blood will be drawn at a moment when blood needs to be drawn using venepuncture for general diagnostics. The venepuncture is already part of the routine laboratory diagnostic care, this is not considered an additional intervention. 30 patients will be included.

To study the role of soluble FLT1 in the severity of clinical features of HHT type 2 the levels of soluble FLT1 will be measured in patient material. To be able to correlate this data to clinical severity we will use the epistaxis severity score (ESS, appendix I) and the HHT severity score (appendix II). The ESS is a validated questionnaire consisting of 6 multiple choice questions. The HHT severity score has not yet been validated but has been used in previous research and consists of a score based on clinical features, this information will be extracted from medical charts.

Study procedures will be performed at the St. Antonius Hospital Nieuwegein and do not interfere with other procedures or protocols. Due to the use of two extra tubes of blood taken during routine sampling, this is not an additional procedure to disease treatment. The venepuncture is already part of the routine laboratory diagnostic care, this is not considered an additional intervention. The blood material will be transferred to the clinical chemistry lab, were the blood will be prepared for transport to the LUMC, Leiden, following the next steps:
1-Collect whole blood into commercially available anticoagulant-treated tubes e.g., EDTA-treated

2-Cells are removed from plasma by centrifugation for 15 minutes at 1,000-2,000 x g using a refrigerated centrifuge (it removes platelets as well). The resulting supernatant is designated plasma.

3-Following centrifugation, it is important to immediately transfer the liquid component (plasma) into a clean polypropylene tube using a Pasteur pipette. The samples should be apportioned into 0.5 ml aliquots, stored, and transported at -20°C or lower. It is important to avoid freeze-thaw cycles.
Residual blood will be discarded safely according to laboratory protocol.
All medical charts will be reviewed and documented in the digital and secured HHT database, that is used for both clinical care and research purposes.
To determine patient characteristics we will use the the epistaxis severity score and the HHT severity score . The ESS is a validated questionnaire consisting of 6 multiple choice questions. The HHT severity score is based on clinical features, this information will be extracted from medical charts.

Study burden and risks

There are no risks or benefits for patients included in this study. There is no compensation. The blood sample is taken during routing venepuncture, does not put the patient in any extra action or risk and standard patient care is followed. Data will only be accessible to HHT-researchers of the St. Antonius Hospital and researchers of the department of nefrology in the LUMC. Data will be filed into a database, where a study number will be assigned to all patients

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 (I) hereditary hemorrhagic telangiectasia type 2 (ACVRL1 mutation) who have been screened previously by the st antonius hospital, HHT centre of exellence, (II) 18 years or older and (III) mentally competent.

Exclusion criteria

None

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-04-2017

Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	31-03-2017
Application type:	First submission
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	NL59720.100.16