Groningen Antithrombin Study

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Objectives: 1. To investigate the types of antitrombin deficiency in these families2. To find the mutations in our families/patients with antitrombin deficiency.3. To establish the risk of VTE due to these mutations and subtypes.(comparing...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Blood and lymphatic system disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON39175

Source
ToetsingOnline

Brief title
GRAS

Condition

- Blood and lymphatic system disorders congenital
- Embolism and thrombosis

Synonym
venous thrombosis and pulmonary embolism

Research involving
Human

Sponsors and support

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

Intervention

Keyword: antithrombin, genetics, VTE

Outcome measures

Primary outcome

1. Number of VTE*s, riskfactors for VTE, treatment for VTE

2. Antithrombin antigen and activity levels

3. Genetic mutations in the SERPINC1 gene

Secondary outcome

• To calculate the absolute and relative risk of VTE in patients with

antithrombine deficiency, compared with non-deficient family members (update

on previous study)

• To describe current anti-coagulant therapy and history of effectiveness and

safety of anti-coagulant therapy

Study description

Background summary

Rationale: Antithrombin deficiency is a rare autosomal dominant prothrombotic disorder. Prevalence of heterozygous antithrombin deficiency is estimated between 1 in 500 and 1 in 5000 persons. (Patnaik et al) Annual incidence of VTE in antithrombin deficient family members of patients with VTE is 1,94% (*1), the risk of recurrent VTE about 10% per year (*2).

Antithombin deficiency can either result from a lack of circulating antithrombin molecules (type 1 deficiency) or from a lack of function of the circulation molecules (type 2 deficiency). The type 2 deficiencies are subdivided according to the localisation of the mutation: type 2 RE (reactive site), type 2 HBS (heparin binding site), type 2 PE (pleiotrophic effects). Patients with a type 2 HBS may have a lower risk of VTE, and therefore this subdivision has clinical impact. (*3)

The antithrombin molecule is encoded in the SERPINC1 gene. Various mutations in patients with antithrombin deficiency were found, most heterozygous, and even some homozygous (Luxembourg et al). Homozygous antithrombin patients are extremely rare, as most homozygous antithrombin mutations are lethal in utero.

The exact protrombotic nature of each mutation however is unknown. The link between genotype and phenotype is often only supported by antithrombine activity measurements in vitro, but not by the study of large families and/or functional studies of the found mutations. Computer models of conformational changes due to mutations are also used, but conflicting in their predictions of clinical importance of mutations (In the study of Luxembourg et al: conflicting results in 8 of 29 analyses). Because of this, no risk can be attributed to a certain mutation.

In the patients and antithrombin-mutated family members studied in our centre (*1,2,4), we found striking differences in our historical data between families and the occurrence of VTE. For example, in one family, in 7 antithrombin deficient family members, no VTE*s occurred, whilst in another family in 10 antithrombin deficient family members 8 VTE*s occurred.
The question arises whether these differences after several years still hold, and - if present - why these differences have occurred. Is this due to antithrombin deficiency subtype, or are there differences within subtypes due to different mutations? Is it possible to describe the exact link between a mutation and clinical behaviour? To investigate these questions, we have formulated the following objectives:

Study objective

Objectives:
1. To investigate the types of antitrombin deficiency in these families
2. To find the mutations in our families/patients with antitrombin deficiency.
3. To establish the risk of VTE due to these mutations and subtypes.(comparing antithrombin deficient family members with non-deficient family members)

Study design

a retrospective family cohort study

Study burden and risks

The amount and number of blood samples: 1 blood sample,
* 10 ml in EDTA (sequencing, MPLA)
* 1x6ml in citrate in previously tested patients (needed for antithrombin activity and antigen measurements)
* 2x6ml in citrate in patients not previously tested (extra tube needed to test other thrombofilic factors which may influence VTE-risk)
the number of site visits: 1
questionnaires or diaries which have to be filled in: 1 questionnaire
physical and physiological discomfort associated with participation: 1 venapuncture,

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

Patient who presented with VTE in our hospital, and were also diagnosed with inherited antithrombin deficieny. (Definition: antithrombin deficiency, measured twice, and also found in at least one family member)
Their family members
Age >= 18 years
Written informed consent

Exclusion criteria

Not applicable

Study design

Design

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

Primary purpose: Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	15-05-2013
Enrollment:	250
Type:	Actual

Ethics review

Approved WMO

Date:	10-01-2013
Application type:	First submission
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	NL41324.042.12