Coagulation and fibrinolysis in patients with resistance to thyroid hormone due to a thyroid hormone receptor β-gene mutation

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To investigate the effect of resistance to thyroid hormone (RTH) due to a TRβ mutation on coagulation and fibrinolysis

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

Summary

ID

NL-OMON38471

Source
ToetsingOnline

Brief title
The THRβ study

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Thyroid gland disorders
- Embolism and thrombosis

Synonym
insensitivity for thyroid hormone because of a change in the DNA, thyroid hormone resistance because of a gene mutation

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: via de SKWOSZ (stichting klinisch wetenschappelijk onderzoek slotervaartziekenhuis

Intervention

Keyword: coagulation, gene mutation, thyroid hormone receptor, thyroid hormone resistance

Outcome measures

Primary outcome

The following groups of lab markers will be tested: labmarkers: thyroid

function and SHBG, coagulation markers and fibrinolysis markers.

Secondary outcome

not applicable

Study description

Background summary

Recent interest has focused on the association between thyroid dysfunction and venous thromboembolism (VTE). Hyperthyroidism is associated with a hypercoagulable state (1-3). Several coagulation and fibrinolytic parameters appear to be affected by thyrotoxicosis; elevated plasma levels of factor VIII (FVIII), factor IX (FIX), von Willebrand factor (VWF), and fibrinogen, and a reduced fibrinolytic activity due to increased levels of plasminogen activator inhibitor-1 (PAI-1) have been reported in both hyperthyroid patients and healthy subjects after taking thyroid hormones (1, 4-10).
A retrospective cohort study was done to determine the risk of VTE in all patients with overt hyperthyroidism and to compare this to the risk of VTE in the general population (11). The incidence rate of VTE in patients with hyperthyroidism appeared to be high.
The exact mechanism of hyperthyroidism leading to affected coagulation and fibrinolytic parameters and thus the hypercoagulable state is unknown. It was shown that in cultured endothelial cells triiodothyronine (T3) induces upregulation of mRNA expression and protein synthesis of VWF, fibronectin (FN) and endothelin-1 (ET-1) (12). The effect of T3 treatment on target gene

regulation was investigated in a thyroid hormone receptor (TR)-overexpressing hepatoma cell line by performing cDNA microarrays (13). Thrombin for example, was multiplied 8-fold by T3 induction and coagulation factor X (FX) 4.9-fold.
We hypothesize that the hypercoagulable state in hyperthyroidism is mediated by the thyroid hormone receptor (TR). Patients with a mutation in the thyroid hormone receptor beta (TRβ) gene have elevated plasma T3 and T4. Therefore, patients with a TRβ mutation can serve as the optimal clinical model to investigate the role of TRβ in the hypercoagulable state seen in patients with hyperthyroidism.

Study objective

To investigate the effect of resistance to thyroid hormone (RTH) due to a TRβ mutation on coagulation and fibrinolysis

Study design

cross-sectional study

Study burden and risks

Blood will be drawn once. Participation in the study will not influence the treatment of the 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 thyroid hormone resistance due to a mutation in the thyroid hormone receptor beta gene
- Elevated T3 and/or T4 according to the local reference ranges;For the control groups:
a) hyperthyroid patients with elevated serum T4 and/or T3 according to the local reference ranges
b) euthyroid controls with general good health, both matched for age (± 5 years) and gender

Exclusion criteria

- No informed consent
- Oral anticoagulant therapy (warfarin, vitamin K antagonists)
- Hemophilia or von Willebrand's disease
- Oral corticosteroid therapy
- Previous VTE within the last 6 months
- Previous thyroid surgery or radio-iodine treatment
- Current anti-thyroid drugs

Study design

Design

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

Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	22-01-2014
Enrollment:	36
Type:	Actual

Ethics review

Approved WMO

Date:	12-12-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL46481.018.13