A novel genetic cause of congenital central hypothyroidism.

Published: 06-05-2015
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Primary objective1) To study the frequency of mutations in this gene in patients with central hypothyroidism and their first- and second-degree relativesSecondary objective: 2) To determine the clinical, biochemical and radiological consequences of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Observational invasive

Summary

ID

NL-OMON43775

Source
ToetsingOnline

Brief title
Genetic cause of central hypothyroidism

Condition

- Hypothalamus and pituitary gland disorders

Synonym
Central hypothyroidism, low blood levels of thyroid hormone because thyroid gland is insufficiently activated

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Central hypothyroidism, Congenital hypothyroidism, Gene, Mutation

Outcome measures

Primary outcome

1) The frequency of mutations of this gene in patients with central hypothyroidism and their first- and second-degree relatives

Secondary outcome

2) Clinical, biochemical and radiological consequences of mutations in this gene for hemizygous (males) and heterozygous (female) carriers:

a. Medical history, including a developmental/psychosocial history

b. Physical examination, including height and weight, pubertal development and thyroid gland size.

c. Biochemical assessment of the HPT axis, including plasma FT4, TSH, T4, T3, rT3, TBG, Tg, TSH bioactivity and a TRH stimulation test.

d. Biochemical assessment of the HP/adrenal axis (plasma cortisol and ACTH), the HP-growth hormone/IGF-1 axis (serum IGF-1 and IGFBP-3), the HP/gonadal axis (plasma LH, FSH + testosterone in males and serum estradiol in females), and the HP/lactotroph axis (plasma prolactin). Pituitary stimulation tests will be performed when indicated.

e. Analysis of pulsatile TSH release

f. Oral glucose tolerance test (OGTT) and homeostatic model assessment (HOMA)

g. Thyroid gland and testicular size measured by ultrasound.

h. Hypothalamus and pituitary morphology assessed by MRI (if possible without any form of anesthesia).

i. Hearing assessment by tone audiometry.

Study description

Background summary

Congenital central hypothyroidism is characterized by insufficient production of thyroid hormone (TH) due to inadequate stimulation by thyroid stimulating hormone (TSH) of an otherwise normal thyroid gland. TH is essential for the growth and development of the brain until the age of 3 years. Untreated congenital central hypothyroidism can lead to irreversible brain damage.

Using whole exome sequencing, a presently unknown gene mutation has been discovered in patients with unexplained congenital central hypothyroidism. The fact that the product of the affected gene plays an important role stimulating the production of thyroid hormone supports our conclusion that mutations in this gene cause congenital central hypothyroidism.

The phenotype in patients with this gene mutations is incompletely known. It is unknown whether these mutations lead to more hormonal deficiencies. The expectation is that more patients with congenital central hypothyroidism are carriers of mutations in this gene. Relatives of these patients are at risk of carrying mutations in this gene, which makes them potential undiagnosed central hypothyroidism patients.

Study objective

Primary objective
1) To study the frequency of mutations in this gene in patients with central hypothyroidism and their first- and second-degree relatives

Secondary objective:
2) To determine the clinical, biochemical and radiological consequences of mutations in this gene in hemizygous (males) and heterozygous (female) carriers.

Study design

Prospective descriptive design

Study burden and risks

Placement of an intravenous cannula and withdrawal of blood (procedures 2e, f) carries a risk of bleeding or bruising. For procedures 2e and 2f subjects will

be admitted to the hospital for several hours. The withdrawal of all thyroid hormone replacement during 24 hours may cause fatigue and constipation. All other procedures are either part of standard patient care, or are non-invasive without further risks.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

- Congenital central hypothyroidism.
- First- or second-degree relative of a patient with congenital central hypothyroidism.

Exclusion criteria

Carrier of other genetic defects known to cause congenital central hypothyroidism.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-07-2015
Enrollment:	25
Type:	Actual

Ethics review

Approved WMO Date:	06-05-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	05-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	07-11-2016
Application type:	Amendment
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	NL52353.018.15