A novel causative gene of congenital central hypothyroidism.

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1) To perform gene mutation analysis in family members of patients carrying a proven mutation in the candidate gene.2) To determine the clinical, biochemical and radiological characteristics of carriers of a mutation in the candidate gene.3) To...

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

Summary

ID

NL-OMON41692

Source
ToetsingOnline

Brief title
Gene mutations in 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, Genes, Mutation

Outcome measures

Primary outcome

1) The genetic sequence of the TBL1X gene in patients with central hypothyroidism.

2) The presence of the same TBL1X-mutation in first- and second degree relatives of patients with a newly discovered TBL1X-mutation.

3) Clinical, biochemical and radiological characteristics of hemizygous (males) and heterozygous (female) carriers of a mutation in the TBL1X gene:

a. Medical history, including a developmental/psychosocial history and attention to hearing impairment.

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

c. 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).

d. Biochemical assessment of liver function (ALAT, ASAT, gamma-GT, glucose, platelet count and albumin).

4)

a. Biochemical assessment of the hypothalamo/pituitary (HP)/thyroid axis,

including plasma FT4, TSH, T4, T3, rT3, TBG, Tg and TSH bioactivity.

b. Hearing assessment by tone audiometry.

c. Thyroid gland and testicular size measured by ultrasound.

Secondary outcome

None

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 Sanger sequencing, a presently unknown gene mutation has been discovered in patients with unexplained congenital central hypothyroidism. The fact that the affected gene plays an important role in the central regulation of the thyroid, makes this gene a likely candidate causative gene of central hypothyroidism. The phenotype in patients with this gene mutations is incomplete. 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.

Hypothesis: via a still unknown mechanism mutations in this gene disrupt the central regulation of the thyroid, leading to a phenotype of biochemical central hypothyroidism.

Study objective

1) To perform gene mutation analysis in family members of patients carrying a proven mutation in the candidate gene.
2) To determine the clinical, biochemical and radiological characteristics of carriers of a mutation in the candidate gene.
3) To compare endocrine, radiological and auditory characteristics of carriers of a mutation in TBL1X to those of their first- and second degree

relatives without a mutation in TBL1X.

Study design

Prospective descriptive design

Study burden and risks

TRH test: intravenous administration of the hormone may induce nausea, urinary urgency or a strange taste in the mouth. This will pass in minutes.
GH-test (adults): intravenous administration of the hormone may induce sweating, drowsiness, palpitations or nausea. In patients with heart disease or epilepsy, an arginin/GHRH test will be performed in stead of a GH-test.
Clonidine (children): intravenous administration of the hormone may induce dizziness, drowsiness and dryness of the mouth.
All mentioned procedures are performed as standard patient care and have a direct therapeutical benefit for all patients.

Placement of an intravenous cannula and withdrawal of blood carries a risk of bleeding or bruising.
The procedures specifically for research (including those performed in non affected relatives) are minimally or non-invasive and have little to no 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

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

Study design

Design

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

Primary purpose: Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	08-04-2014

Enrollment:	50
Type:	Actual

Ethics review

Approved WMO Date:	12-03-2014
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	03-03-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	06-05-2015
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	NL47462.018.13