Clinical assessment of patients with a mutation in the IGSF1 gene

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This is a protocol aimed at standardizing clinical care and the diagnostic approach in a carrier of a pathogenic IGSF1 mutation referred for hormonal analysis to the outpatient clinic.

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

Summary

ID

NL-OMON41375

Source
ToetsingOnline

Brief title
Clinical assessment IGSF1

Condition

- Hypothalamus and pituitary gland disorders
- Testicular and epididymal disorders

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

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Clinical, IGSF1, Patients

Outcome measures

Primary outcome

1. Medical history.

2. Physical examination.

3. DEXA or bioelectrical impedance analysis for body composition.

4a. Fasting blood sample for FT4, FT3, T3, TSH, prolactin, LH, FSH, testosterone, SHBG, inhibin B, antimüllerian hormone, oestradiol, DHEAS, DHEA, androstenedione, IGF-I, IGFBP-3, cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, glucose, insulin, C-peptide, cortisol, ACTH, GH, leptin.

4b. TRH-induced response of TSH, prolactin and growth hormone at 0*, 20*, 60*, 90*, 120*, 180*. Free T4, Free T3 and thyroglobulin will be determined at 0, 120 and 180 minutes. TSH bioactivity will be assessed at 0, 20 and 60 minutes.

4c. If clinically indicated: GnRH-induced response of LH and FSH; GH response to GH stimulation test; and assessment of corticotrope axis.

5. Ultrasound examination of the thyroid gland, and testis or ovaries.

6. Echocardiography

Secondary outcome

1. Ring size

2. X-ray of hand

3. Photograph with conventional camera

4. Questionnaire assessing complaints related to growth hormone overproduction

5. Neuropsychological tests

For participation in these measurements, the patient will receive a financial

compensation.

Study description

Background summary

Recently a novel X-linked syndrome caused by loss of function of IGSF1 was discovered (Sun et al., Nature Genetics 2012). In IGSF1 deficient males, the syndrome is characterized by central hypothyroidism in all patients (26 in 11 families), macroorchidism in all males (from late adolescence), hypoprolactinaemia in 18/26 patients, partial and transient growth hormone (GH) deficiency in 4/26 patients, disharmonious pubertal development, obesity, and elevated serum IGF-I in late adulthood. Out of 20 female heterozygous carriers of an IGSF1 mutation, five were hypothyroid, and in at least two female carriers ovarian cysts were observed. Serum IGF-I was elevated in the majority of these females.

The clinical significance of the syndrome, particularly the clinical consequences of untreated hypothyroidism and elevated serum IGF-I, justifies to screen family members of patients with an IGSF1 mutation for carriership, and to study potential carriers of IGSF1 mutations, including patients with central hypothyroidism, combined GH and TSH deficiency, macroorchidism, or delayed puberty. If found positive, the clinical assessment should be performed in a standardized fashion, and the results should be communicated to the medical community. It is not unlikely that the clinical, laboratory and radiologic characteristics are more diverse than suggested by the findings in the first set of patients.

Study objective

This is a protocol aimed at standardizing clinical care and the diagnostic approach in a carrier of a pathogenic IGSF1 mutation referred for hormonal analysis to the outpatient clinic.

Study design

Prospective descriptive study

Study burden and risks

The small risk of minor side-effects related to the endocrine function tests are largely outweighed by the fact that these tests are part of standard

clinical care, and they are directly aimed at assessing what treatment the patient requires.

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

Documented pathogenic mutation in the IGSF1 gene
Informed consent

Exclusion criteria

None

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):	07-10-2013
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO Date:	12-06-2013
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	23-09-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	09-10-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO	

Date:	31-10-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	20-11-2013
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
Approved WMO Date:	04-02-2015
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)

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	NL42991.058.13