The prevalence of the IGSF-1 mutation in children who develop central hypothyroidism after starting Growth Hormone treatment.

Published: 23-04-2013
Last updated: 24-04-2024

1) Follow-up study of project 2011_371:To determine whether the 27 children found in this study actually had a central hypothyroidism, by complementing the existing data with details from the medical records. The data used in the first study were...

Ethical review	Approved WMO
Status	Will not start
Health condition type	Hypothalamus and pituitary gland disorders
Study type	Observational invasive

Summary

ID

NL-OMON38491

Source
ToetsingOnline

Brief title
The prevalence of the IGSF-1 mutation

Condition

- Hypothalamus and pituitary gland disorders

Synonym
hypothyroidism, too little thyroid hormones

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Growth Hormone treatment, Hypothyroidism, IGSF-1 mutation

Outcome measures

Primary outcome

- To gather the exact medical data of the 27 children who are being treated with thyroxine, to confirm that they were diagnosed with central hypothyroidism. (based on the concentrations of FT4 and TSH before starting with GH)

- To evaluate growth velocity and compare this with children diagnosed with isolated growth hormone deficiency.

- To determine the prevalence of the occurrence of the IGSF-1 mutation in children which develop a central hypothyroidism after start of GH.

Secondary outcome

N.V.T.

Study description

Background summary

In children with suspected isolated GH deficiency (GHD), the free thyroxine (FT4) concentrations may fall after starting with hormone (GH) treatment. This central hypothyroidism could be the result of unmasking an already existing (mild) central hypothyroidism by giving GH. Consequently, this could indicate the existence of (congenital) multiple anterior pituitary insufficiency rather than an isolated GHD. With this in mind, we hypothesized that children who develop central hypothyroidism after starting GH, already had lower thyroxine concentrations at birth compared to children with true isolated GHD. To confirm this hypothesis, a previous study was performed (2011_371): 'The thyroid hormones after starting Growth Hormone treatment in children.

The aim of this study was to compare the T4 concentrations of children with a 'real' isolated GHD, measured during the neonatal screening, compared with children who developed central hypothyroidism after starting GH.
For this purpose written informed consent was received from 369 children diagnosed with GHD in 41 national medical centers. Of these 369 children information was retrieved from the RIVM and the Foundation for Child and Growth. This information showed that 27 children after starting with GH were treated with thyroxine. Moreover, we found that children who did not receive thyroxine after start with GH have an higher T4 average at the neonatal screening than children with central hypothyroidism (- 0.31 SD (n = 127) versus -1.3 SD (n = 5)). These data are clinically relevant because these children probably already have an congenital central hypothyroidism and may benefit with earlier detection and treatment.
Recently, a new gene is discovered, the IGSF-1 gene, which may be responsible for the existence of a central hypothyroidism. In these children GHD can also be present.

Study objective

1) Follow-up study of project 2011_371:
To determine whether the 27 children found in this study actually had a central hypothyroidism, by complementing the existing data with details from the medical records. The data used in the first study were obtained from the database of the Foundation for Child and Growth. These data were provided by the treating pediatricians to the Foundation and are measured at baseline, after 1 year and 2 years of GH therapy. We included all children in the group if a decrease in FT4 was seen in the period from 0 to 2 years after starting GH treatment. However, the exact moment of decline in FT4 concentrations is unknown to us. we are also not informed on the precise laboratory data just before starting T4 . Our hypothesis that the growth velocity in children who need thyroxine after starting with GH is lower than children who don't need thyroxine is not answered by the lack of sufficient data.
For this reason, further research is needed in medical files; firstly to definitively establish that these 27 children started with thyroxie for diagnosing central hypothyroidism (indicating the precise laboratory values ** at the time of start GH). Also, it is necessary to collect data for confirming the hypothesis that these children had a slower growth rate from the moment of starting GH due to co-existing ypothyroidism, compared to children who don't need thyroxine treatment. From the parents of these 27 children, currently only informed consent was asked and received for the retrieval of information known to the Foundation for Child and Growth and the RIVM where neonatal screening results are saved, but not to gather data from the medical files of the corresponding hospital.

2) The prevalence of the mutation in the IGSF-1 gene in children who develop central hypothyroidism after starting with GH.
In response to the article "Loss-of-function mutations in IGSF1 cause an

X-linked syndrome of central hypothyroidism and testicular enlargement ', we would like to do a follow-up study with the 27 cases from our previous study (after confirmation of the fact that there was a central hypothyroidism and not a thyroidal hypothyroidism). The neonatal screening results of these children show that the 27 children treated with T4 after starting with GH already had low-normal values of their thyroid function during neonatal screening. This confirms that there is actually a (mild)congenital central hypothyroidism, with later in life developing (or discovering) of GHD. In this recently published study a corresponding loss of function mutation in the IGSF-1 gene is discovered in different families. This gene causes central hypothyroidism discovered at different ages and in some cases, is accompanied with a GHD. The researchers noticed also testicular enlargement and variable prolactin values**.
The purpose of this second part of the study is to investigate the prevalence of the IGSF-1 gene mutation in the 27 children known with central hypothyroidism after starting with GH.

Study design

(1) Follow-up study of project 2011_371: To determine whether the 27 children had central hypothyroidism with additional data from the medical records.
After receiving informed consent, information from the medical records will be gathered upon the laboratory values **before and during treatment with thyroxine and about the growth velocity before and after starting thyroxine.
The burden for the patient in this case is minimal. For this information, the treating pediatricians will be contacted.

(2) Prevalence of IGSF-1 mutation
The 27 children all use growth hormone and thyroxine. For this reason they have to visit their treating pediatrician every 4 to 6 months . During this visit blood samples are also collected to check the thyroid values**. Testing for the presence of the IGSF-1 mutation may therefore occur during a routine blood collection.
Informed consent will be asked to draw an additional blood sample for testing the presence of an IGSF-1 mutation.

Study burden and risks

The burden for the patients is very low. Data collection from the medical file will be done anonymous and does not harm the patient.
The determination of the possible presence of the IGSF-1 mutation is not considered a burden for the patient, because this will be determined in a blood sample that is already collected for routine patient care.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Children (2-11 years)

Inclusion criteria

Children receiving thyroxine within two years after starting growth hormone treatment.

Exclusion criteria

Children with isolated Growth Hormone deficiency (not using thyroxine) or children already known with Multiple Pituitary Hormone deficiency at the moment of starting growth hormone treatment.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Will not start
Enrollment:	27
Type:	Actual

Ethics review

Approved WMO

Date:	23-04-2013
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	NL43978.018.13