Immunological and adrenal function in children with CHARGE syndrome

Published: 20-09-2013
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Our primary objectives are:- to estimate the prevalence of central adrenal insufficiency , defined as a plasma cortisol response

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

Summary

ID

NL-OMON38436

Source
ToetsingOnline

Brief title
Immunological and adrenal function in CHARGE syndrome

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Adrenal gland disorders
- Immunodeficiency syndromes

Synonym
CHARGE syndrome

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Fonds NutsOhra

Intervention

Keyword: CHARGE syndrome, CHD7, Immunologic Deficiency Syndromes, Pituitary-Adrenal System

Outcome measures

Primary outcome

The main study parameters are:

- the absolute numbers of immunological cells and concentration of

immunoglobulins;

- functional T-cell response and specific antibody concentration;

- the absolute numbers of T cell rearrangement excision circles (TRECs);

- RNA profile of genes involved in the immunological pathways; and

- the maximum level of cortisol in the low-dose ACTH test.

The main study outcomes are:

- the presence of immune dysfunction

- the presence of central adrenal insufficiency

Secondary outcome

The secondary study parameters are:

(1) clinical signs and symptoms of immune dysfunction based on a questionnaire

and

(2) type of CHD7 mutation. CHD7 mutations are classified as truncating (i.e.

nonsense, frameshift, deletions, and genomic rearrangements) and non-truncating

mutations (missense, splice site) and are known for the 40 study participants.

Study description

Background summary

Coloboma of the eye, Heart defects, Atresia of the choanae, Retardation of growth and/or development, Genital abnormalities, Ear abnormalities and deafness (CHARGE) syndrome is caused by a de novo dominant mutation in the CHD7 gene. Truncating mutations in the CHD7 gene are, in general, associated with a more severe phenotype compared to non-truncating mutations.
CHARGE syndrome has a high morbidity and we noticed unexplained mortality in our own CHARGE population. CHARGE syndrome shares many features with 22q11.2 deletion syndrome, a syndrome that often shows immunological dysfunction. CHARGE syndrome also shares features, in particular hypothalamic-pituitary hormonal disorders, with Prader-Willi syndrome. In the latter syndrome central adrenal insufficiency has been demonstrated, a condition that influences morbidity and mortality.
Thus, the aim of the study is to explore whether immune dysfunction and central adrenal insufficiency are part of the complex phenotype of CHARGE syndrome, and thus eventually may contribute to its morbidity. Since it has been noticed that children with CHARGE syndrome due to a truncating mutation have in general a more severe phenotype than children with a non-truncating mutation, we will compare our immunological observations in both groups. If central adrenal dysfunction is found, we will correlate this observation with the type of mutation (i.e. dysfunction is more frequently seen in children with truncating versus non-truncatng mutations). The results of this study will enable us to indicate whether future studies are needed to underpin evidence*based guidelines for appropriate diagnostic immunological and adrenal function testing and surveillance or treatment in patients with CHARGE syndrome.

Study objective

Our primary objectives are:
- to estimate the prevalence of central adrenal insufficiency , defined as a plasma cortisol response <500 nmol/l in the low-dose ACTH test (see paragraph 8.3.5 of the protocol).
- to describe immune dysfunction, i.e. whether individual immunological parameters deviate from normal and if so, which parameters
- to estimate the prevalence of immune dysfunction
in children with CHARGE syndrome due to a CHD7 mutation.

Secondary, we want
- to describe whether there is a relation between the immunological laboratory outcomes and
o the presence or absence of clinical signs of immune dysfunction based on a questionnaire

o the genotype, i.e. truncating versus non-truncating mutation in CHD7 in children with CHARGE syndrome.
- to correlate central adrenal insufficiency with type of CHD7 mutation, i.e. whether central adrenal indufficiency is more often seen in children with CHARGE syndrome due to a truncating mutation than due to a non-truncating mutation
- to indicate whether future studies are needed to underpin evidence-based guidelines for appropriate diagnostic testing and surveillance or treatment of immune and adrenal function disorders in patients with CHARGE syndrome.
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Study design

The study is an observational cross sectional study. For some of the immunological testing a case-control design will be used.

Study burden and risks

Children with CHARGE syndrome may benefit from the immunological and adrenal function tests as timely diagnosis of insufficient immunological and adrenal function may result in prevention of complications. The risk and burden associated with the study can be considered negligible and minimal, respectively. All participants will have to visit the hospital for half a day. Study participants will have to fill-out a structured questionnaire (15-20 minutes). They will undergo a short physical examination. An intravenous peripheral catheter will be inserted (total blood sampling 12-15 ml). The healthy control group will have to fill-out a simplified questionnaire (5-10 minutes). Only height and weight will be measured. A single venous puncture of 3 ml blood will be performed. Both the adrenal function test and the immunological tests are validated tests and are used in routine patient diagnostics. Appropriate medical care and surveillance will be offered to all participants with abnormal study results. This study can only be performed in children with CHARGE syndrome as explained in the rationale. A control group is needed to significantly increase the reliability of the outcome parameters in the study participants.

Contacts

Public
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL

Scientific
Universitair Medisch Centrum Groningen

Hanzeplein 1
Groningen 9713 GZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

For patients:
- Age above 20 months (after full immunization program) and below 18 years.
- Proven CHARGE syndrome due to a CHD7 mutation.
For controls:
- Age above 20 months and below 18 years.
- Sibling of a CHARGE patient as defined above.

Exclusion criteria

For patients:
- The use of steroids or other medication that can interfere with immunological or adrenal function.
- Any signs of infection at time of tests
For controls:
- The use of steroids or other medication that can interfere with immunological or adrenal function.
- ENT problems (under surveillance of an ENT specialist, adenoidectomy, tympanostomy tubes, otitis media with effusion) in the last two years.

- Any signs of infection at time of tests

Study design

Design

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

Primary purpose: Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	16-10-2013
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	20-09-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-02-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Not approved Date:	01-02-2016
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	NL45445.042.13