Extreme Lipid Phenotypes in Autosomal Dominant Hypercholesterolemia: The ELePHANT Study

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1) To investigate the underlying mechanisms of the variable ADH phenotypes in two extreme ADH populations. - Genetically homozygous patients with a phenotype resembling the phenotype encountered in heterozygous ADH patients. - Genetically…

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

Summary

ID

NL-OMON40882

Source
ToetsingOnline

Brief title
The ELePHANT Study

Condition

- Chromosomal abnormalities, gene alterations and gene variants

Synonym
Autosomal Dominant Hypercholesterolaemia, Inherited Hypercholesterolaemia

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Eigen afdeling;reserve budget van onder andere Nederlandse Hartstichting Beurs

Intervention

Keyword: Autosomal Dominant Hypercholesterolemia, Phenotypes

Outcome measures

Primary outcome

1) Identification of novel (epi) genetic causes of extreme ADH phenotypes.

2) Carotid IMT measurements:

- The mean difference in age and gender adjusted cIMT between the two extreme ADH populations.

- The mean difference in age and gender adjusted cIMT between the separate ADH populations and their first and second degree relatives.

Secondary outcome

- Mean difference in age and gender adjusted cIMT between molecularly defined homozygous and molecularly defined heterozygous ADH patients matched for age, gender and plasma LDL-C levels. To reach this endpoint, homozygous ADH patients in our cohort will be matched with heterozygote ADH patients in whom a cIMT measurement was previously performed (METC 07/138#).

Study description

Background summary

Autosomal Dominant Hypercholesterolemia (ADH) is characterized by sharply elevated plasma LDL-C levels and is caused by mutations in LDLR, APOB and/or PCSK9.
Homozygosity for mutations in these genes is commonly considered to result in an extreme clinical phenotype (LDL-C levels above 13mmo/L). In a recent study, however, we observed that LDL-C levels were considerably lower in 50% of the patients with molecular defined homozygous ADH.
In contrast; in 0.05% of all heterozygous ADH patients (with an expected LDL-C

level in the range 5-8 mmol/L) we observed LDL-C levels that were considerably higher and based on clinical criteria, one would these patients classify as hoADH. This exemplifies the disconnect between the molecular diagnosis and the clinical phenotype. Aim of our study is to identify (epi) genetic and biological factors underlying these extremes in phenotypical variation. Moreover, vascular imaging studies will be performed to study the consequences of the dyslipidemia in these two patient cohorts. This will contribute to a new definition of homozygous ADH.

Study objective

1) To investigate the underlying mechanisms of the variable ADH phenotypes in two extreme ADH populations.
- Genetically homozygous patients with a phenotype resembling the phenotype encountered in heterozygous ADH patients.
- Genetically heterozygous patients who were presented with a phenotype similar to the clinical phenotype seen in clinical homozygous ADH patients

2) To study the vascular consequences of these extreme ADH phenotypes by using cIMT measurements.

Study design

Observational cross-sectional study

Study burden and risks

This study does not involve interventions with significant risk for participating individuals. The only risk exists of possible development of a haematoma on the injection site, after blood sampling and possible development of a scar on the side of the skinbiopsy. Measurement of carotid Intima Media Thickness is a non-invasive procedure using ultrasonography.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

I) Individuals with molecular defined homozygous ADH (two molecular defects in two different alleles in the ADH causing genes (LDLR, APOB or PCSK9)) without the clinical phenotype for homozygous ADH (LDL-C < 13 mmol/L). OR
II) Patients heterozygous for ADH causing mutations AND a phenotype compatible with clinical homozygous ADH (LDL-C levels > 13 mmol/L without lipid lowering therapy or LDL-C levels > 7.8 mmol/L while receiving maximal dose of a statin and ezetimibe) (according to the clinical criteria for homozygous ADH).

Exclusion criteria

Indication of another clinical condition that (in the opinion of the investigator) might explain the extreme ADH phenotype
I) Thyroid dysfunction
II) Renal insufficiency
III) Cholestasis
IV) Alcohol use
V) Use of medication known to impact lipid metabolism (including but not limited to psychopharmacologic therapeutics, protease inhibitors, beta blockers, thiazide diuretics).

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	19-06-2014
Enrollment:	1100
Type:	Actual

Ethics review

Approved WMO

Date:	17-04-2014
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	NL47764.018.14

Study results

Date completed:	29-08-2018
Actual enrolment:	20