Lipid storage in Fabry disease and Acid Sphingomyelinase deficiency

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Metabolic and nutritional disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON50314

Source
ToetsingOnline

Brief title
Lipid storage in Fabry disease and Acid Sphingomyelinase deficiency

Condition

- Metabolic and nutritional disorders congenital
- Inborn errors of metabolism

Synonym
Fabry diseases or alpha-galactosidase-A-deficiëncy. Acid Sphingomeylinase Deficiency (ASMD) or NIemann PIck type B

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,subsidie stichting Stofwisselkracht ;20.000 euro

Intervention

Keyword: Acid Sphingomyelinase deficiency, Fabry Disease, Lipid storage, recombinant HDL

Outcome measures

Primary outcome

Primary study parameter(s)

· HDL composition and plasma LCAT activity

· LDL receptor activity and abundance

· SREBP signalling

· Lipid content of lysosomes and endosomes in fibroblasts

· Response of the above parameters to incubation with recombinant HDL

The above mentioned parameters will be measured in plasma and fibroblasts.

Patients will be compared to healthy subjects, and untreated fibroblasts will

be compared to fibroblasts incubated with rHDL

Secondary outcome

not applicable

Study description

Background summary

Fabry disease (FD) and Acid sphingomyelinase deficiency (ASMD) , also known as Niemann Pick disease type B, are both inherited lysosomal storage diseases where the inherited deficiency of lysosomal *-galactosidase and acid sphingomyelinase leads to the accumulation globotriaosylceramide (Gb3) and sphingomyelin (SM) respectively. Enzyme replacement therapy (ERT) is an established treatment for FD , for ASMD therapy with recombinant human acid sphingomyelinase is currently under clinical evaluation.
Cholesterol accumulation also plays an important role in both FD and ASMD . It

was recently shown that cholesterol accumulation can be alleviated by enhancing ABCA1 mediated efflux in both Fabry disease and ASMD .
With these study we aim to further characterize the altered cholesterol metabolism in these patients and asses whether objective is to assess whether treatment of FD and ASMD fibroblasts with recombinant HDL can relieve the intracellular accumulation of cholesterol.

Study objective

The objective of this study is to further characterization the cholesterol pathways leading to storage of not only globotriaosylceramide (Gb3) en sphingomyelin (SM) in respectively Fabry disease and ASMD but also of storage of cholesterol in these diseases. We will focus on plasma LCAT activity and HDL composition; SREBP-signaling and LDL-receptor abundance and activity ; lipid content of lysosomes and endosomes in fibroblasts.
Furthermore we aim to develop a new treatment strategy to break the vicious cycle of GB3, sphingomyelin and cholesterol accumulation with recombinant high density lipoprotein using a cellmodel of Fabry disease and ASMD: by using cultured fibroblasts and treating these wit recombinant HDL the ABCA1-mediated efflux of cholesterol if facilitated which leads to reduced lipid storage.

Study design

This is a single center cohort study to further characterize cholesterol pathways and the effects of treatment with recombinant HDL in patients with FD , ASMD and healthy subjects.

Study burden and risks

The risks of blood collection through venipuncture and skin biopsy are considered minimal but may include soreness, bleeding or infection. In total about 55,4 blood will be collected (2x 10 ml in EDTA-tube, 2x 10 ml in HGEL-tube, 1x 10 ml in serum-tube, 2x 2,7 ml in citrate-tube)

In the participating FD and ASMD patients, blood sample collection and will be performed during routine check-up visits. Patients will be asked to fast overnight prior to their routine visit and study blood collection through venipuncture will be combined with those as part of the routine visit. Fibroblasts of participating FD and ASMD patients will be obtained from the AMC biobank metabolic diseases. Patient will not directly benefit from participation.

Healthy subjects that participate in this study will not benefit from participation. They will be asked to fast overnight before study visit. The single study visit consist of a blood draw through venipuncture and a skin biopsy. Due to the extent of this study certain findings in healthy subjects

might call for further medical evaluation. Depending on the follow up may require additional tests or medical procedures as indicated, and/or referral to the general physician or a medical specialist.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

General good helath as determined by medical history
The individual is willing and able to provide signed informed consent prior to study-related procedures
The individual is > 18 years of age, In case of a patient with FD or ASMD: a confirmed diagnosis of FD or ASMD and presence of fibroblasts

Exclusion criteria

For patients and healthy subjects:
- Unwillingness to adhere to study protocol , For healthy subjects only
- Medical history of hypercholesterolemia or other lipid disorder
- Use of cholesterol lowering medication

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:	Recruiting
Start date (anticipated):	12-06-2017
Enrollment:	42
Type:	Actual

Ethics review

Approved WMO

Date:	17-05-2017
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	NL61039.018.17