A pilot study to explore plasma abnormalities as possible biomarkers in patients with acid sphingomyelinase deficiency (ASMD)

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Primary objectiveTo investigate the presence of plasma abnormalities in treated and untreated patients with ASMD to determine whether they can potentially serve as useful biomarker . Therefore we will determine- sphingolipids and *metabolites-...

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

Summary

ID

NL-OMON43166

Source
ToetsingOnline

Brief title
Plasma biomarkers in ASMD

Condition

- Metabolic and nutritional disorders congenital
- Inborn errors of metabolism

Synonym
acid sphingomyelinase deficiency (ASMD), Niemann Pick disease type B

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W,subsidies bij Stofwisselkracht en Metakids zijn aangevraagd;eventuele toewijzing is nog niet bekend ten tijde van indiening

Intervention

Keyword: Acid sphingomyelinase deficiency, biomarkers, Niemann Pick type B

Outcome measures

Primary outcome

Presence and changes in plasma abnormalities regarding sphingolipid

metabolites, macrophage/inflammatory markers, markers of lung involvement,

lipid profiles and oxysterols in treated and untreated ASMD patients during a

period of 24 months.

Secondary outcome

not applicable

Study description

Background summary

Acid sphingomyelinase deficiency (ASMD), also known as Niemann Pick disease type A and B, is a rare lysosomal storage disease characterized by an autosomal recessive inherited deficiency of acid sphingomyelinase (ASMase). This results in lysosomal accumulation of sphingomyelin (SM) primarily in macrophages. In addition, recent research indicates that this defect influences the proper function of the endosome-lysosome system. Key feature is the accumulation of sphingolipids, predominantly SM as well as cholesterol in spleen, liver, lungs and other organs .
The pathophysiology of ASMD is only partially understood. Key feature is the formation of pathological lipid-laden macrophages in spleen, liver and lungs and other organs which likely leads to a chronic low-grade inflammatory state as demonstrated by slightly elevated ceramide levels in these patients. The close connection between levels of SM, ceramide and endosomal/lysosomal

cholesterol transport suggests that altered cholesterol transport also impacts lysosomal storage of SM and related sphingolipids.
Treatment consists of supportive care. However, enzyme replacement therapy with recombinant human acid sphingomyelinase is currently under clinical evaluation in the ASCEND trial, an international phase II/III randomized controlled trial in which the AMC is a participating center.This potential new treatment option is an excellent opportunity to explore the presence of plasma abnormalities which may prove to be of value in the identification of potential biomarkers.

Study objective

Primary objective
To investigate the presence of plasma abnormalities in treated and untreated patients with ASMD to determine whether they can potentially serve as useful biomarker . Therefore we will determine
- sphingolipids and *metabolites
- macrophage markers chitotriosidase and CCL-18
- pro- and anti-inflammatory cytokines
- surfactant protein A and D, KL-6, YKL-40 , CC16 and cCK18 as markers of pulmonary involvement
- lipid profiles including cholesterol, HDL, LDL and apolipoproteins as well as the oxysterols 7-KC and C-triol

Study design

This pilot-study is a prospective observational study of a cohort of ASMD patients , both untreated patients and patients receiving enzyme replacement therapy as part of the ASCEND trial. All ASMD patients known in the Academic Medical Center (AMC) will be contacted to participate in this study. In this study plasma abnormalities will be studied in ASMD patients over a period of 24 months. The amount of frequency of additional plasma samples is dependent on when a patient is also participating in the ASCEND trial.

In untreated patients plasma samples will be obtained every 6 months during a period of 24 months. This will be scheduled on the same day as their routine appointments, which often already includes a blood collection through venipuncture.
In treated patients, who will be receiving infusions every other week as part of the ASCEND trial, additional plasma samples will be drawn.
For analysis of sphingolipids and *metabolites , macrophage markers, cytokines and oxysterols 2 ml of extra blood will be drawn at week 0,10,14,26 and 52 right before during and directly after infusion as well as 1 hour, 4 hours, 8 hours and 24 hours after infusion.
To determine markers of lung involvement 14ml of blood will be drawn right before infusion at week 0 , 52, 80 and 104. Finally 4,5 ml of extra blood for lipid profiles will be obtained right before and 24 hours after infusion at

week 0, 26, 52, 80 and 104.

Study burden and risks

Patients participating in this study will all be diagnosed with ASMD and therefore will visit our hospital regularly for routine check-ups. When patients are also participating in the ASCEND enzyme replacement trial they will visit our hospital regularly since they will be receiving infusions every two weeks For this pilot study we require additional blood samples to be collected during routine check-up visits or study visits. Therefore no extra site visits for this study are necessary and when possible blood collections through venipuncture will be combined with those as part of a routine (study) visit.
The risk of blood collection through venipuncture is considered minimal but may include soreness, bleeding or infection .

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

1. The patient is willing and able to provide signed informed consent prior to study-related procedures.
2. The patient is *18 years of age.
3. The patient has been diagnosed with ASMD.

Exclusion criteria

Unwillingness to participate

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	02-01-2017
Enrollment:	10
Type:	Actual

Ethics review

Approved WMO Date:	23-12-2016
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	NL59522.018.16