Fasting tolerance in patients with medium-chain acyl-CoA dehydrogenase deficiency (MCADD) in the first six months of life: an investigator-initiated human pilot-study.

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Inborn errors of metabolism
Study type	Observational invasive

Summary

ID

NL-OMON48331

Source
ToetsingOnline

Brief title
FiTtINg MCADD: Fasting Tolerance In MCADD-infants.

Condition

- Inborn errors of metabolism

Synonym
Fatty-acid oxidation disorder, inborn error of metabolism

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Groningen
Source(s) of monetary or material Support: Universitair Medisch centrum Groningen: de Junior Scientific Masterclass en het PoLiMeR consortium. Stichting Stofwisselkracht is aangeschreven als additioneel fonds.

Intervention

Keyword: Biomarkers, Fasting tolerance, MCADD

Outcome measures

Primary outcome

• Symptoms and signs of perturbed glucose homeostasis;

• Signs of increasing lipolysis.

Secondary outcome

• Dynamics of physiological parameters;

• Dynamics of blood-gas-analysis;

• Dynamics of remaining targeted metabolites in plasma and urine;

• Dynamics of (untargeted) multi-omics (metabolomics, lipidomics, and

proteomics) parameters.

• (Untargeted) multi-omics (metabolomics, lipidomics, and proteomics) of

hepatocytes, derived from induced-pluripotent stem cells (iPS), established

from lymphocytes;

• (When applicable) Dynamics of CGM-data.

Study description

Background summary

MCAD deficiency (MCADD; #OMIM 201450) is the most common inborn error of

mitochondrial fatty acid oxidation. Already before the introduction of population newborn bloodspot screening (NBS), large phenotypic heterogeneity was observed between MCADD patients, ranging between deceased patients and asymptomatic subjects. Most clinically ascertained patients were homozygous for the common c.985A>G ACADM mutation. After the introduction of the disorder to the NBS, newborns with novel ACADM-genotypes have been identified. Subjects can be classified as either severe/classical or mild/variant MCADD patients.
Dietary management guidelines are based on expert opinion and limited experimental data summarized in one retrospective study on fasting tolerance in 35 MCADD-patients. Interestingly, data are absent on the fasting tolerance of MCADD patients between 0-6 months of age. These guidelines cause parental stress, especially regarding young patients (0-6 months). Moreover, the guidelines do not take into account the heterogeneity between patients, including the classification between severe versus mild MCADD patients. The investigators question whether at least a subset of the MCADD patients is overtreated with these guidelines.

Study objective

The main objective of the study is to explore the fasting tolerance in MCADD patients of two and six months of life. Second, it is aimed to compare fasting tolerance and biochemical dynamics between subsets of MCADD patients. Third, it is aimed to identify novel diagnostic and/or prognostic biomarkers or fasting tolerance. The last objective is to elucidate the (fundamental) origin of phenotypical differences between MCADD patients.

Study design

Longitudinal, prospective, investigator-initiated human pilot-study.

Study burden and risks

The trial is considered to be a low-risk study. The clinical research team at the UMCG has a longstanding tradition of performing supervised controlled clinical fasting test in patients with inborn errors of metabolism, for diagnostic as well as research purposes. No adverse effects are expected during fasting in otherwise healthy infants with MCADD. The study holds three moderate burdens for participants: insertion of the indwelling IV catheter, the discomfort of fasting for the subject and the parent(s) or guardian(s), and the time consumption. However, subjects and their parents(s) may directly benefit from the results of this study by reduction of stress concerning feeding, under normal, healthy circumstances. Furthermore, the treating metabolic pediatrician may provide an (individualized) feeding regimen based on the results of the supervised clinical fasting tests. As this project will substantiate current management guidelines and aims to identify new (prognostic) biomarkers, it may further improve the outcomes of future MCADD patients and their parent(s) or

guardian(s), by reduction of (unnecessary) parental stress, treatment and follow-up.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Children (2-11 years)

Inclusion criteria

1. Age below 6 months of life. In case of premature births, the child may be included and treated according to the corrected age.;2. Established MCADD diagnosis. The diagnosis should be confirmed by a combination of (a) NBS outcome (b) MCAD enzyme activity measured with phenylpropionyl-CoA as a substrate, ideally in lymphocytes (considered to be the golden standard) and (c) ACADM gene mutation analysis.

Exclusion criteria

Any other chronic and/or genetic condition that is deemed an exclusion criterion based on the judgement of the treating metabolic paediatrician or investigators.

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	22-05-2019
Enrollment:	20
Type:	Actual

Ethics review

Approved WMO

Date:	24-04-2019
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

Approved WMO

Date:	05-07-2022
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
ClinicalTrials.gov	NCT03761693
CCMO	NL68011.042.19