Evaluation of genetic, enzymatic, biochemical and clinical characteristics of OCTN2/CPT2/CACT/BKT deficiency to determine if new born screening is useful and feasible

Published: 19-06-2019
Last updated: 17-01-2025

To survey the clinical and biochemical characteristics of individuals diagnosed with OCTN2, CPT2, CACT or BKT deficiency or suspected with OCTN2 deficiency after NBS in the Netherlands to aid the decision on whether or not to include these disorders...

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

Summary

ID

NL-OMON52401

Source
ToetsingOnline

Brief title
OCTN2/CPT2/CACT/BKT Deficiency Implementation in Newborn screening: ODIN

Condition

- Inborn errors of metabolism

Synonym
Carnitine Uptake Disorder (CUD), Primary Carnitine Deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Utrecht
Source(s) of monetary or material Support: ZonMW

Intervention

Keyword: Carnitine, Fatty acid oxidation and carnitine shuttle, Newborn screening, OCTN2 deficiency

Outcome measures

Primary outcome

The main study outcome is survey of OCTN2, CPT2, CACT or BKT deficiency in the

Netherlands based on the following study parameters:

- Clinical data; Medical history, current clinical state, physical examination.

- Biochemical data; Laboratory assays performed in the context of diagnosis, eg

acylcarinitine profile, protein activity, gene analysis, glucose/ketone level,

CK level.

- Additional testing; All additional tests performed in the context of

evaluation of the disorder, eg electrocardiogram, cardiac ultrasound, imaging.

Secondary outcome

Sensitivity, specificity, positive predictive value and negative predictive

value of novel functional assay, measuring OCTN2 transporter activity in

cultured skin fibroblasts and lymfocytes.

Study description

Background summary

OCTN2 deficiency, CPT2 deficiency, CACT deficiency and BKT deficiency are all inborn errors of metabolism that result in impairment of oxidation of long chain fatty acids or their products (ketone bodies). They all have a varying clinical spectrum ranging from asymptomatic *individuals* to patients presenting with hypoglycemia, neurodevelopmental delay, (cardio)myopathy and/or cardiac arrhythmia which may lead to sudden death. Currently, CPT2, CACT and BKT deficiency are only diagnosed after symptoms have arisen, OCTN2 deficiency can also be identified in the Dutch newborn screening (NBS) program as a secondary finding when the acylcarnitine profile is obtained to detect other inborn errors of fatty acid metabolism. It is considered an unintended finding. For all four conditions, it is currently unclear whether all individuals that would be identified by NBS should be considered patients and if treatment is necessary, or whether, at least a subset of the identified individuals have a benign biochemical and genetic variant and will remain asymptomatic. Cases or case series in the literature often lack detailed information, are relatively old or not representative of the situation in the Netherlands.
For OCTN2 deficiency, an additional obstacle in the workup of newborns with low carnitine levels in NBS is the fact that these levels can reflect maternal levels as a consequence of placental transmission of carnitine. In this case the true levels of the newborn are initially unclear, diagnosis is not yet possible and retesting needs to be performed a few weeks later. The low levels of carnitine in newborns may reflect primary carnitine deficiency in the mother, or more rarely, another inborn error of metabolism (IEM) resulting in low carnitine. These mothers are almost all asymptomatic and whether these incidentally discovered deficiencies represent a true health risk and require treatment and follow-up is unclear. A comprehensive guideline as to how physicians should act upon the finding of a low carnitine level in NBS does not yet exist in the Netherlands. For OCTN2, CPT2, CACT and BKT deficiency a full overview of the characteristics of all (current and historical) patients in the Netherlands is necessary to be able to come to an informed decision whether or not to include these disorders in the Netherlands newborn screening program.

Study objective

To survey the clinical and biochemical characteristics of individuals diagnosed with OCTN2, CPT2, CACT or BKT deficiency or suspected with OCTN2 deficiency after NBS in the Netherlands to aid the decision on whether or not to include these disorders in the newborn screening program.

Study design

Retrospective and prospective cohort study

Study burden and risks

Participation in this study bears no significant risks, as most collected data

are obtained as part of standard care. In addition to the blood sample taken for regular care 2ml blood is taken. For adults this will be a blood sample of 5ml blood.
Furthermore, the study is aimed towards improvement of newborn screening, optimizing health benefit and limiting unnecessary referrals, treatment and anxiety. To improve the newborn screening program, it is essential and inevitable to include children that underwent newborn screening in its current form (since 2007). Additionally, for CPT2/CACT and BKT-deficiency, it is essential and inevitable to include children that are diagnosed with these disorders, in order to achieve a complete picture of these disorders in the Netherlands.

Contacts

Public
Universitair Medisch Centrum Utrecht

Lundlaan 6
Utrecht 3584 EA
NL
Scientific
Universitair Medisch Centrum Utrecht

Lundlaan 6
Utrecht 3584 EA
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)

Elderly (65 years and older)
Babies and toddlers (28 days-23 months)
Newborns
Premature newborns (<37 weeks pregnancy)

Inclusion criteria

• OCTN2 deficiency, confirmed by reduced carnitine transporter activity in cultured fibroblasts and/or mutations in the SLC22A5 gene.
• Subject referred to academic centre for OCTN2 deficiency because of low carnitine level in NBS.
• Mother analysed in academic centre for OCTN2 deficiency due to low carnitine level in infant*s NBS.
• CPT2 deficiency, confirmed by reduced Carnitine palmitoyltransferase II activity in lymphocytes or cultured fibroblasts and/or biallelic mutations in the CPT2 gene.
• CACT deficiency, confirmed by carnitine acylcarnitine translocase activity in cultured fibroblasts and/or biallelic mutations in the SLC25A20 gene.
• BKT deficiency, confirmed by reduced 2-methylacetoacetyl-CoA thiolase activity in cultured fibroblasts and/or biallelic mutations in the ACAT1 gene.

Exclusion criteria

No exclusion criteria. All subjects that meet inclusion criteria are elligible for inclusion

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Health services research

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	06-08-2019

Enrollment:	380
Type:	Actual

Ethics review

Approved WMO Date:	19-06-2019
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	31-07-2019
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	30-07-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	20-10-2020
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	19-08-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	28-06-2022
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	18-01-2023
Application type:	Amendment
Review commission:	METC NedMec

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	NL67683.041.19