Hypomagnesemia as mitochondrial disease

Published: 04-11-2019
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The main objective is to investigate whether the variant indeed cause mitochondrial dysfunction leading to the observed phenotype, including characterization of the pathophysiology.

Ethical review	Approved WMO
Status	Completed
Health condition type	Renal and urinary tract disorders congenital
Study type	Observational invasive

Summary

ID

NL-OMON48233

Source
ToetsingOnline

Brief title
Magmidi

Condition

- Renal and urinary tract disorders congenital
- Electrolyte and fluid balance conditions
- Renal disorders (excl nephropathies)

Synonym
inherited disease, Magnesium deficiency

Research involving
Human

Sponsors and support

Primary sponsor: Radboud Universitair Medisch Centrum
Source(s) of monetary or material Support: Ministerie van OC&W

Intervention

Keyword: Genetic disease, Hypomagnesemia, Mitochondrial DNA

Outcome measures

Primary outcome

The primary study parameters are:

- Mitochondrial function of patient cells compared to reference values, control cells from healthy unrelated individuals and cells of other affected families (obtained from collaborators)

- Response of patients to a thiazide diuretic challenge test compared to the normal population (matched for age and gender)

- Fractional excretion of magnesium in patient urine compared to reference values

Secondary outcome

The secondary study parameters are:

- The correlation between mitochondrial function of a patient*s fibroblasts and the serum magnesium concentration of the patient

- Heteroplasmy level of the mtDNA variant in blood, urine and fibroblasts of participants (i.e. what is the percentage of mtDNA carrying the abnormal variant in different tissues)

- Score at NMDAS (Newcastle Mitochondrial Disease Adult Scale), (Schaefer et al., 2006)

- Laboratory parameters as listed in Table 1 of the Research protocol. Results will be retrieved from the patient record by the treating physician and pseudonymously shared with the researchers. When the necessary evaluations are

not available, blood will be drawn for these laboratory evaluations at

Radboudumc. Values will be compared to normal reference values for each

analysis.

Study description

Background summary

Hypomagnesaemia (a serum magnesium concentration below 0.7 mmol/L) is a common medical disorder that can lead to cramps, tiredness, seizures and in very severe cases coma or death. Causes of hypomagnesaemia include gastro-intestinal malabsorption or loss, use of certain drugs and specific genetic disorders. Excessive loss of magnesium through renal magnesium wasting is a hallmark of all the currently known genetic causes. In approximately 90% of cases, it is possible to pinpoint the hypomagnesaemia to a specific molecular cause, while the remainder of suspected genetic cases is still unsolved. In this study, we aim to investigate a rare variant in the mitochondrial genome (m.4291T>C) that might explain part of the remaining 10%. Several unrelated families with this variant exhibit renal magnesium wasting. We hypothesize that this variant leads to impaired mitochondrial function and subsequent dysfunction of the mitochondrion-rich distal convoluted tubule.

Study objective

The main objective is to investigate whether the variant indeed cause mitochondrial dysfunction leading to the observed phenotype, including characterization of the pathophysiology.

Study design

Case series

Study burden and risks

The overall risk of the study is primarily determined by the thiazide challenge test. The most severe complications related to administration of thiazide compounds encompass dehydration, hypokalemia, hypo-/hypernatremia and an allergic reaction to hydrochlorothiazide. By the choice of test (i.e. a test that has been used in clinical practice before), the careful monitoring plan, execution at a department with experience in thiazide challenge tests and the supervision by an experienced nephrologist, we believe that the risk of this study will be kept to an acceptable minimum. We do not expect any serious

adverse events to happen. The METC previously gave approval for the use of this test in another research proposal, and the test was subsequently implemented in clinical practice. The rest of the study carries little risk but some burden, i.e. collecting 24-hour urine and a hospital visit of one day. During this day, the patient would undergo three blood draws, one skin biopsy to obtain fibroblasts, and fill out the Newcastle Mitochondrial Disease Adult Scale together with a doctor.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Being a carrier of the m.4291T>C variant in the mitochondrial DNA.

Exclusion criteria

- Age below 16 years
- Lacking competency to make personal medical decisions (in Dutch: *wilsonbekwaam*)

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	23-01-2020
Enrollment:	12
Type:	Actual

Ethics review

Approved WMO

Date:	04-11-2019
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL70750.091.19

Study results

Date completed:	23-01-2020
Results posted:	06-10-2021
Actual enrolment:	2

First publication
06-10-2021