

Metabolic derAngements in heReditary multiple Exostoses (HME) subjects with either heterozygous EXT1 or EXT2 mutations; a clinical cohort study (MARE study)

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We would like to study whether aberrant heparansulfate synthesis in HME subjects leads to impaired glucose metabolism, dyslipidemia and subsequent increased cardiovascular risk as well as impaired adrenal gland function when compared to unaffected...

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

Summary

ID

NL-OMON37615

Source

ToetsingOnline

Brief title

MARE study

Condition

- Metabolic and nutritional disorders congenital
- Glucose metabolism disorders (incl diabetes mellitus)

Synonym

adrenal insufficiency, diabetes mellitus

Research involving

Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum

Source(s) of monetary or material Support: ZONMW (veni beurs dr M. Nieuwdorp)

Intervention

Keyword: adrenal gland insufficiency, EXT mutations, hereditary multiple exostoses, type 2 diabetes mellitus

Outcome measures

Primary outcome

Changes in glucose metabolism (oral glucose tolerance tests) in subjects with HME with either EXT1 or EXT2 mutation compared to unaffected control subjects.

Secondary outcome

Changes in cardiovascular risk (lipid profile and ECG changes) in subjects with HME with either EXT1 or EXT2 mutation compared to unaffected control subjects.

Changes in adrenal gland function (synacthen test) in subjects with HME with either EXT1 or EXT2 mutation compared to unaffected control subjects.

Study description

Background summary

EXT-1 or EXT-2 genes are of pivotal importance in normal organ and skeleton development due to their role in heparansulfate synthesis, a sugar chain present in all human cells. Hereditary multiple exostoses (HME) is a clinical syndrome comprising lifelong risk of development of cartilage/bone tumor formation and therefore are regularly checked at the OLVG orthopaedic outpatient clinic. Previous research from our group has shown that HME subjects are characterized by impaired insulin secretion, a hormone involved in glucose metabolism. Moreover, we found that mice with EXT1 or EXT2 heterozygous mutations (eg murine model of human HME) are characterized by dyslipidemia/fasting hypertriglyceridemia due to impaired cholesterol uptake in the liver. Moreover, we gathered evidence that heparansulfates are implicated in normal adrenal function, a gland that synthesizes cortisol. In order to

investigate whether these findings hold true for HME subjects with either EXT1 or EXT2 mutations or unaffected family member, we would like to execute this study.

Study objective

We would like to study whether aberrant heparansulfate synthesis in HME subjects leads to impaired glucose metabolism, dyslipidemia and subsequent increased cardiovascular risk as well as impaired adrenal gland function when compared to unaffected family members.

Study design

observational study with functional (oral glucose tolerance test and synacthen) tests

Study burden and risks

Despite a minimal risk of short term hypotension upon synacthen bolus infusion, no sideeffects are expected. Moreover, we believe that the outcome of these three studyquestions regarding glucose tolerance, cardiovascular risk and adrenal gland function categorized to EXT1 or EXT2 genotype renders usefull information for phenotype and clinical status of subjects with HME. Moreover, we think that these results provide pathophysiological information about glucose tolerance, cardiovascular risk and adrenal gland function in the general population. Therefore we think that the benefits of this study outweigh the minimal conveyed risk.

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

*Age between 18 and 70 years

*Clinical diagnosis of Hereditary Multiple Exostoses (HME) with/without proven EXT1/EXT2 mutation (patient) OR unaffected family member (control)

*Written informed consent

Exclusion criteria

* History of psychiatric disease (psychosis)

* Pregnancy or female participants at childbearing age not using adequate contraception (due to synacthen infusion)

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: Recruitment stopped
Start date (anticipated): 05-07-2012
Enrollment: 400
Type: Actual

Ethics review

Approved WMO
Date: 23-02-2012
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 | NL38725.018.12 |
| Other | NTR 10510 |