Study of the neuromuscular and multisystem features of patients with malignant hyperthermia or rhabdomyolysis related to a RYR1 variant

Published: 07-07-2020
Last updated: 08-04-2024

Primary Objective: There are three primary objectives in this study. 1. To investigate the neuromuscular involvement of RYR1 related MH and rhabdomyolysis. 2. To investigate the immunological changes in subjects with RYR1 related MH and...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Muscle disorders
Study type	Observational invasive

Summary

ID

NL-OMON50075

Source
ToetsingOnline

Brief title
Multisystem features of malignant hyperthermia and rhabdomyolysis

Condition

- Muscle disorders

Synonym
Muscle breakdown by exercise and high body temperature by anesthetics

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: Malignant hyperthermia, Multisystem features, Rhabdomyolysis, RYR1

Outcome measures

Primary outcome

The study consists of three parts. Each part has it*s own main study

parameters

1. Clinical part: the results of the questionnaire study compared to

standardizes normal values and the results of the comprehensive clinical

assessment and creatinine kinase levels

2. Imaging part: fatty infiltration and hypertrophy of proximal and axial

muscles.

3. Immunological part: circulating and leukocyte released anti- and

pro-inflammatory cytokine levels compared to healthy age and sex matched

controls.

Secondary outcome

Not applicable

Study description

Background summary

Malignant hyperthermia and rhabdomyolysis are phenotypes that have long been considered to occur only in response to external stimuli (trigger anaesthesia and physical exhaustion) show several features of a continuous disease manifestation. Previous studies showed prolonged bleeding time after injury, selective immunological advantages, axial muscle weakness and several social difficulties. A detailed study of the neuromuscular and multisystem features of

patients with RYR1-related malignant hyperthermia or rhabdomyolysis is needed to provide clarification about the continuous and multisystem disease manifestations in these patients.

Study objective

Primary Objective: There are three primary objectives in this study.
1. To investigate the neuromuscular involvement of RYR1 related MH and rhabdomyolysis.
2. To investigate the immunological changes in subjects with RYR1 related MH and rhabdomyolysis.
3. To identify multisystem features of RYR1 related MH and rhabdomyolysis.
There are no secondary objectives.

Study design

The design of the study will be a clinical, open, observational study. The study consists of three parts; a clinical, imaging and immunological part.

Study burden and risks

Malignant hyperthermia and rhabdomyolysis are severe and potential life threatening medical conditions. Recent studies show growing evidence for multisystem involvement of RYR1 variants associated with malignant hyperthermia. In parallel, next generation sequencing has identified a rapidly expanding number of RYR1 variants with uncertain pathogenicity based on segregation analysis and prediction models. Knowledge about multisystem involvement of RYR1 variants may be used for future counselling and informing patients, future development of new research and/or treatment strategies.

The effort to participate is relatively small when taking the risks of malignant hyperthermia and rhabdomyolysis into account. One visit to the Radboudumc will be needed, for taking blood samples, performing neurological examination, functional assessment, history taking muscle MRI and muscle ultrasound.
This study can be classified as a study with a negligible risk. Blood samples will be taken through venepuncture, a procedure with only minor risks.

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

* A history of malignant hyperthermia susceptibility (MHS), confirmed by diagnostic RYR1 variant or IVCT related to a RYR1 variant and/or a history of rhabdomyolysis related to a variant in RYR1
* Minimum age 18 years old.

Exclusion criteria

* Patients diagnosed with a neuromuscular disease resulting in muscle weakness (apart from RYR1 related rhabdomyolysis and malignant hyperthermia).
* Patients with symptoms of angina pectoris.
* Patients with contra-indications for MRI-scan are excluded.
Contra-indications for MRI-scan include metallic implants (vascular clips, foreign bodies like metallic splinters in the eye, coronary and peripheral artery stents, prosthetic heart valves, pacemakers and ICD*s, cochlear implants, breast tissue expanders and some other electronic implants or devices and known claustrophobia.
* Current malignancy
* Pregnancy or lactating

* Other health issues whereby patients are not able to fulfil the study protocol
* No written informed consent by the patient

Specific exclusion criteria for participating in the immunological part of the study (patients excluded for the immunological part of the study can take place in the other parts)
* Diabetes mellitus
* Patients currently using medicine affecting the immune system.
* Patients with a compromised immunity (e.g. HIV)

* Patients with a history of auto-immune disease (e.g. SLE, psoriasis, IBD)
* Use of statins the past year
* Use of systemic corticosteroids during more than two weeks in the past 5 years
* Previous treatment with chemotherapy and/or radiation therapy

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	19-08-2020
Enrollment:	60
Type:	Actual

Ethics review

Approved WMO Date:	07-07-2020
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-04-2021
Application type:	Amendment
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	NL72351.091.20