The role of genetic factors in the aetiology of achalasia

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Primary:- To identify causal genetic variants and proteomes involved in achalasia and to study their relevanceSecundary:- To build-up a large scale harmonized biobank of achalasia patients, based on combining existing and new data from the European...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Gastrointestinal motility and defaecation conditions
Study type	Observational invasive

Summary

ID

NL-OMON39386

Source
ToetsingOnline

Brief title
Genetics in achalasia

Condition

- Gastrointestinal motility and defaecation conditions
- Neuromuscular disorders

Synonym
Achalasia, Oesophageal motility disorder

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Achalasia, Aetiology, Genetics, Proteomics

Outcome measures

Primary outcome

Genetic variants associated with achalasia.

Secondary outcome

Demographic and clinical data on idiopathic achalasia.

Study description

Background summary

Achalasia is rare motility disorder of the oesophagus of which the pathofysiolofy is still lagerly unknown. There is a progressive destruction and degeneration of the neurons in the myenteric plexus which causes aperistalsis of the oesophageal body and dysrelaxation of the lower oesophagus sphincter (LOS). The exact cause of the alterations in the myenteric plexus remains to be determined. Genetic, infectious, neuodegenerative and autoimmune mechanisms have all been suggested as possible etiological factors. Achalasia leads to severe symptoms, the patients have an increased risk for development of carcinoma of the oesophagus and currently treatment is purely palliative. Therefore further insight into the aetiology of achalasia is important because it can drive the search for new targets for therapy, diagnostics and prevention of achalasia.

Accumulating data suggest a role for genetic factors in the pathofysiolgy of achalasia. Studies have suggested that patients with achalasia may have a certain genetic background that leads to an autoimmune response resulting in the destruction of the neurons. It is likely that the genetic background of achalasia shows a similar pattern to that of other rare diseases with a suspected autoimmune aetiology such as systemic scleroderma. Furthermore an increased risk for development of achalasia has been observed in monozygotic twins and siblings of patients with achalasia. The observation that there is an increased risk of developing achalasia in certain genetic disorders supports, together with the other data, the hypothesis that certain genetic factors play an important role in the development of achalasia. Therefore it is important to do further research into genetic variants that are possible associated with achalasia which also leads to further insight into the aetiology of the

disease.

Study objective

Primary:
- To identify causal genetic variants and proteomes involved in achalasia and to study their relevance

Secundary:
- To build-up a large scale harmonized biobank of achalasia patients, based on combining existing and new data from the European and Non-European centres.
- To perform large scale genetic studies to identify the most likely causal common and rare genetic variants for achalasia.
- To study the functional relevance of identified genetic variants in achalasia using genomics and proteomics.
- To integrate genetic, genomics and proteomics into clinical phenotypes and course of the disease.

Study design

A prospective observational study, in a multicentre setting.

Study burden and risks

The study subjects will donate once 20 mL of venous blood by means of a standard venapuncture. A venapuncture for blood withdrawal is a safe procedure and routinely performed in the clinical setting, with rarely any serious complications. There is no serious risk attachted. Small complications are a bleeding or a puncture hematoma for which no treatment is necessary. In rare cases patients get an infection or a thrombophlebitis after a venapuncture, which seldom needs treatment. The venapuncture will be performed by a trained nurse or physician who are qualified to perform venapunctures and therefore complication will be kept to a minimum.

Study subjects that undergo a surgical or endoscopic myotomy for the treatment of achalasia will be asked to give informed consent for taking 6 biopsies of the oesophageal muscle layers during the procedure. The duration of the myotomy will not be extended due to the biopsy. Taking biopsies during a surgical or endoscopic myotomy is a regular performed procedure and rarely gives complications. A qualified and trained surgeon or gastroenterologist will take the biopsies. A rare but potentially severe risk of a biopsy is a perforation. In most cases a perforation can be treated expectatively, directly during the procedure or endoscopically. In a minority of cases, surgery has to be performed to close the perforation. Another very rare risk of an oesophageal biopsy is a bleeding, which can be treated directly during the procedure or endoscopically.

Furthermore participants will be asked to complete a questionnaire for demographic and clinical data, which isn't associated with any risks.

From the blood samples of the study subjects, DNA and plasma will be isolated. A Genome Wide Association analysis (GWAS) and Next-Generation Sequencing will be performed on the DNA and proteomics on the plasma. The biopsies of the oesophageal muscle layers will also be used for proteomics. The DNA analysis enables the sequencing of the entire genome and in that way information will be obtained that contains all coding regions, exones of each participant. Not all variants in all exones will be evaluated, the results in patients with achalasia will be compared to one another in order to find variants in genes they have in common. Therefore the chance for unexpected findings is small but it still exists. It may be that variants are found in genes that are not only associated to achalasia but are also associated with an increased chance of developing another disorder. Participants are informed about this, and need to agree to be informed about such results if the findings have significant consequences for their health and care. Participants will only be informed about disorders that can be influenced by medical interventions or interventions into their life style. An increased risk in developing disorders that cannot be prevented by medical or life style intervention will not be reported to the participants. Study subjects who refuse to be informed about such factors cannot participate in the study. So, in conclusion study subjects are at risk, because the whole DNA is analysed, that certain medical information is coming up that they wouldn't have known otherwise. However, the risk is relatively small.

The risks of the additional acts and studies are minimal for the study subjects. The results of the study have no consequences for the participants and don't influence the treatment or the prognosis of the disease. The study can provide new insights in the aetiology of achalasia and possibly offer new targets for therapy and diagnosis, which may benefit all patients with achalasia in the future. Because the risks for the study subjects in this study are minimal and the results of the study can give valuable, new information about the aetiology of achalasia it is justified to perform this study.

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

- Diagnosis of idiopathic achalasia confirmed by oesophageal manometry that show the following criteria:
- Aperistalsis or simultaneous contractions in the oesophageal body.
- LOS dysrelaxation.
- Age *18 years.
- Written informed consent.

Exclusion criteria

- Having a medical or mental contradictory condition to participate in the study, even after agreeing to participate.
- Pseudoachalasia.
- Upper gastrointestinal malignancy.
- Chagas disease.
- Previous allogeneic bone marrow transplant.
- Non leukocyte depleted whole blood transfusion within 120 days of the date of genetic sample collection.

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):	31-08-2012
Enrollment:	450
Type:	Actual

Ethics review

Approved WMO Date:	27-08-2012
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-01-2014
Application type:	Amendment
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	NL40570.018.12