Differences in the genetic coding for HFE, HMOX1 and haptoglobin, important in handling of iron and haem, in relation to the severity of haemophilic arthropathy

Published: 09-04-2013
Last updated: 24-04-2024

The aim of the study is to evaluate whether these three genetic characteristics are able to predict the susceptibility to joint damage in haemophilia patients. Therefore we want to determine the association between the progression of radiographic...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Chromosomal abnormalities, gene alterations and gene variants
Study type	Observational invasive

Summary

ID

NL-OMON41231

Source
ToetsingOnline

Brief title
Iron / haem handling and haemophilic arthropathy

Condition

- Chromosomal abnormalities, gene alterations and gene variants
- Joint disorders

Synonym
bleeding disorder, haemophilia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Cartilage, Haem, Haemophilia, Iron

Outcome measures

Primary outcome

The main parameters that are measured are the presence of an HFE gene mutation, the length of the (GT)n-repeat in the promoter region of the HMOX1 gene and the genotype of Hp. These parameters will be related to progression in radiographic joint damage, measured as amount of increase in Pettersson score/year; the latter from consisting retrospective databases from the patients involved.

Secondary outcome

The number of joint bleeds per year as recorded by patients in general practice, the age at first joint bleed and the severity of the haemophilia have an effect on joint damage progression and might confound the relation of the differences in genetic coding for iron and haem handling and joint damage.

Study description

Background summary

In the genetic bleeding disorder haemophilia, recurrent joint bleeds lead to specific changes in synovium and cartilage called haemophilic arthropathy. There is an unexplained variation in the susceptibility to joint damage. Even with a similar bleeding pattern, the amount of radiological joint damage differs between patients.
It is shown that haemoglobin and its degradation products haem and iron are important factors contributing to this joint damage. Impaired clearance of iron

from the joint might play a role in developing more severe joint damage. Several mechanisms might be involved. In this study we focus on three genetically determined mechanisms (polymorphisms). 1) A pilot study in haemophiliacs suggested the association between carriership of a haemochromatosis gene (HFE) mutation and the severity of haemophilic arthropathy. 2) A possible mechanism of protection against haem-induced damage is haem-oxygenase (HO)-1 that breaks down haem. The length of a guanine-thymidine (GT)n-repeat in the promoter region of the gene encoding HO-1 (HMOX1) determines the level of HO-1 induction. A long (GT)n-repeat (n-repeat * 25) resulting in less HO-1 expression, is in rheumatoid arthritis associated with more severe joint damage. 3) There may be protection of joint damage by the haemoglobin-scavenging molecule haptoglobin (Hp). There are two alleles of the Hp gene coding for three different phenotypes; Hp2-2 has a lower haemoglobin binding ability compared to the other two phenotypes, suggesting more susceptibility to blood-induced joint damage.

Study objective

The aim of the study is to evaluate whether these three genetic characteristics are able to predict the susceptibility to joint damage in haemophilia patients. Therefore we want to determine the association between the progression of radiographic joint damage and these three genetic characteristics: carriership of an HFE mutation, the (GT)n-repeat length within the HMOX1 promoter region, and the Hp genotype.

Study design

The study is designed as a cross-sectional study to collect biomaterials, using retrospectively collected longitudinal clinical data, and without an intervention performed. Severe haemophilia patients visit the Van Creveldkliniek on a regular base, two to three times a year, and moderate haemophilia patients at least once a year. During these visits blood is taken for regular care activities to perform routine tests, e.g. to determine the development of inhibitors against factor VIII/IX. When blood is drawn for these routine tests, patients are asked to give an additional 3x10ml blood for the proposed study.

Study burden and risks

There are no considerable risks or direct benefits for the patients. In general care X-rays to determine radiological damage are made routinely at least every 5 years by the Van Creveldkliniek and registration of joint bleeds in a diary is standard. An additional 3x10ml blood is taken for research purposes of the present study during a visit at the Van Creveldkliniek at the time of regular blood sampling for patient care, routinely by a nurse dedicated to venipuncture by these patients.

The final outcome of the study may lead to a change in prophylactic treatment of patients to prevent bleedings even better in those with the highest risk of damage.

Contacts

Public
Academisch Medisch Centrum

Heidelberglaan 100
Utrecht 3584 CX
NL
Scientific
Academisch Medisch Centrum

Heidelberglaan 100
Utrecht 3584 CX
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

Patients with severe and moderate haemophilia (factor VIII/IX activity *5%) of 18 years or older who visit the Van Creveldkliniek regularly and are treated according to the Van Creveld protocol.

Exclusion criteria

None

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	21-06-2013
Enrollment:	284
Type:	Actual

Ethics review

Approved WMO Date:	09-04-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)
Approved WMO Date:	12-02-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Utrecht (Utrecht)

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	NL42808.041.12