Is there a relation between the P blood group status and Fabry disease severity?

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The following research questions were formulated:• Does blood group P status (presence or absence of the 42C>T-SNP) correlate to GB3 content on fibroblasts and white blood cells of healthy controls?• Does blood group P status correlate to (lyso)...

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

Summary

ID

NL-OMON39730

Source
ToetsingOnline

Brief title
P blood group and Fabry disease

Condition

- Metabolic and nutritional disorders congenital

Synonym
Fabry disease

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Blood group P, Fabry disease

Outcome measures

Primary outcome

Part one: amount of mRNA of GB3 synthase as measured by RT-PCR on fibroblast and white blood cells and GB3 amount as measured by HPLC.

Part two: correlation between plasma lyso (GB3) and P blood group status, Fabry disease severity as measured by FOS-SSI and age at onset of first clinical event by Kaplan Meier analysis.

Secondary outcome

NA

Study description

Background summary

Fabry disease (OMIM 301500) is an X-linked lysosomal storage disease caused by a deficiency of the lysosomal enzyme alpha-galactosidase A1. This enzyme is essential in the degradation of certain glycosphingolipids (predominantly GB3, also known as blood group antigen Pk) and as a consequence Fabry patients accumulate these glycosphingolipids. Lipid accumulation occurs in many cell-types, including the vascular endothelium which in turn is thought to cause progressive renal insufficiency, cardiac hypertrophy and cerebral infarctions, which are often seen in this disorder2. The Fabry phenotype is very heterogeneous, and the contributing factors to this broad expression are poorly understood. The lack of a reliable predictor for disease severity troubles predicting individual prognosis, and hampers decisions about treatment indication.
One hypothesis to explain the phenotypic variability is that the synthesis and presence of GB3 in cells might differ between Fabry patients (e.g. the more GB3 a Fabry patient synthesizes, the more they may suffer from Fabry disease). Recently a single nucleotide polymorphism (SNP 42C>T) in the

GB3 synthase (*-1,4-galactosyltransferase, A4GALT) gene was discovered which influences the correct splicing of the GB3 synthase mRNA leading to lower levels of the enzyme and consequently to decreased levels of GB3 and other glycosphingolipids on erythrocytes 3. Presence or absence of the 42C>T-SNP determines an individual's blood group P status (e.g. erythrocyte GB3 expression). The P status can now be defined as P1P1, P1P2 or P2P2, where P2P2 has less GB3 erythrocyte surface expression than P1P1 and P1P2 intermediate GB3 surface expression.
Though blood group P status correlates with GB3 content on erythrocytes it is unknown how it influences GB3 status on other cell types. We hypothesized that, if blood group P correlates with GB3 content on all cells, blood group P status could be a predictor of GB3 burden and predict phenotype heterogeneity in Fabry disease. To test our hypothesis we chose to examine this in fibroblasts for practical reasons: they were yet available in a biobank of the lab Genetisch Metabole Ziekten (with informed consent). White blood cells of healthy controls are necessary to see whether data of Thuresson et al. 3 are reproducible.
An earlier study in Fabry patients could not find a correlation between blood group P status and Fabry disease severity 4. However, this study determined blood group P serologically, which is less precise than the genetic determination. Further restrictions of this study were a small Fabry cohort and the lack of a disease severity classification. Also the relation of blood group P to different cell types was not investigated.

Study objective

The following research questions were formulated:
• Does blood group P status (presence or absence of the 42C>T-SNP) correlate to GB3 content on fibroblasts and white blood cells of healthy controls?
• Does blood group P status correlate to (lyso) GB3 in plasma or urine of Fabry patients?
• Does blood group P status correlate to Fabry disease severity?

Study design

This study consists of two parts. Part one is an observational laboratory study on white blood cells and fibroblasts of healthy subjects. Part two is an observational retrospective cohort analysis on (existing) clinical and biochemical data (DNA, Fabry biomarkers) of Fabry patients. The data of Fabry patients was earlier collected for routine health care.

Study burden and risks

Participation in this study has no direct advantage for the participants. However, the risks associated with venapunctions are negligible and little

physical or psychological discomfort associated with participation is expected.

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

1. The healthy volunteer is willing and able to provide signed informed consent prior to study-related procedures.
2. The healthy volunteer is >=18 years of age.

Exclusion criteria

1. Use of anticoagulants (e.g. vitamin K antagonist)

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):	26-02-2013
Enrollment:	30
Type:	Actual

Ethics review

Approved WMO

Date:	17-01-2013
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	NL42458.018.12