The transferrin saturation/hepcidin radio: a study on the diagnostic value in the differentiation of Iron Refractory Iron Deficiency Anemia from Iron Deficiency Anemia

Published: 19-09-2017
Last updated: 15-04-2024

We aim to validate the TSAT/hepcidin ratio as a diagnostic tool with a high specificity and to establish a cut off point in order to discriminate between Iron Refractory Iron Deficiency Anemia (IRIDA) and iron deficiency anemia (IDA) not because of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematological disorders NEC
Study type	Observational invasive

Summary

ID

NL-OMON50596

Source
ToetsingOnline

Brief title
SATURNUS study

Condition

- Haematological disorders NEC

Synonym
Iron Refractory Iron Deficiency Anemia (IRIDA)

Research involving
Human

Sponsors and support

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

Intervention

Keyword: - hepcidin, - Iron Deficiency Anemia (IDA), - Iron Refractory Iron Deficiency Anemia (IRIDA), - transferrin saturation

Outcome measures

Primary outcome

The main study outcome is a cut off point for the TSAT/hepcidin ratio that discriminates IRIDA from iron deficient anemia (IDA) because of other reasons than IRIDA with a high specificity.

Secondary outcome

The study will generate data on the mean and interquartile ranges of the TSAT/hepcidin ratio of the IRIDA patients (n=17) and the mean and interquartile ranges of the TSAT/hepcidin ratio of the control group diagnosed with IDA because of other reasons than IRIDA.
The data on the TSAT/hepcidin ratios in controls with IDA because of other reasons than IRIDA will be compared with data on TSAT/hepcidin ratios in healthy individuals that have been established earlier in order to determine if there is any difference between these groups (Galesloot et al).

Bi-allelic and mono-allelic TMPRSS6 variants may be found in the control patients that have been referred to gastro-enterologist or gynaecologist for analysis of IDA. In these control patients IDA has been incorrectly exclusively attributed to gastrointestinal or gynaecological blood loss and/or

malabsorption since IRIDA has not been considered earlier.

Study description

Background summary

The transferrin saturation (TSAT)/hepcidin ratio could be a useful diagnostic tool in diagnosing patients with Iron Refractory Iron Deficiency Anemia (IRIDA). IRIDA is an inherited disorder caused by defects in TMPRSS6. Matriptase-2, encoded by TMPRSS6, plays an essential role in down-regulating hepcidin, the key regulator of iron homeostasis. Pathogenic TMPRSS6 mutations result in uninhibited hepcidin production, causing IRIDA, a disease characterized by a microcytic, hypochromic anemia not (properly) responding to (especially oral) iron supplementation.
Until now, sequencing the exons of TMPRSS6 for pathological variants has been the gold standard for diagnosing IRIDA. However, DNA studies are expensive and not always conclusive. Our case series on the genotype-phenotype correlation in IRIDA patients and their relatives support the notion that phenotypical penetrance of TMPRSS6 defects is influenced by other (epi)genetic and environmental factors such as growth, co-morbidity as inflammation and blood loss, corroborating some previous observations in mice and man.On the other hand, patients with a clinical phenotype of IRIDA, might lack an IRIDA genotype (clinical observations, data not shown).
Since the cardinal feature of IRIDA is a discrepantly high serum hepcidin in relation to the low iron body status, we hypothesize that the TSAT/hepcidin ratio could be a useful diagnostic tool. In our small study population, consisting of clinically presenting patients and their relatives, TSAT/hepcidin ratio was able to discriminate between bi-allelic and mono-allelic IRIDA patients, and between mono-allelic IRIDA patients and their phenotypically unaffected relatives with the same heterozygous TMPRSS6 defect, even after iron supplementation had been given, provided that inflammation was absent. However, before its introduction as a diagnostic test in the work up of iron deficient microcytic anemic patients suspected for the presence of IRIDA, the ratio needs confirmation in phenotypically and genotypically proven IRIDA patients versus patients presenting with an iron deficient microcytic anemia because of other reasons, e.g., inadequate intake, blood loss or other forms of refractory IDA, such as celiac disease, autoimmune gastritis, and Helicobacter pylori.

Study objective

We aim to validate the TSAT/hepcidin ratio as a diagnostic tool with a high specificity and to establish a cut off point in order to discriminate between Iron Refractory Iron Deficiency Anemia (IRIDA) and iron deficiency anemia (IDA)

not because of IRIDA.

Study design

Observational study

Study burden and risks

Participation in this study involves the collection of 11 ml blood at one time point, apart from standard diagnostic procedures. Therefore the risks and burden for the subjects can be considered as minimal.
Subjects will not receive any compensation or treatment because of participation in the SATURNUS study and will not directly benefit from inclusion. However, by participating in this study, subjects will contribute to the development of a new diagnostic tool that will differentiate between IRIDA and other causes of IDA.
There is a small chance a pathologicalTMPRSS6 variant is found in the participants. When a participant has a pathological mono-allelic of bi-allelic TMPRSS6 variant this means that he/she has a (mild) form of IRIDA, which might explain the IDA, either or not in combination with other causes as blood loss or malabsorption. This information is relevant since an explanation for IDA might prevent an extensive work-up for IDA and since the diagnosis of IRIDA has clinical consequences (parenteral iron required in most cases). Moreover, IRIDA is a genetic, inherited disease. Diagnosis of IRIDA in the participant will allow screening of first grade relatives for the presence of genotypic/phenotypic IRIDA.

Contacts

Public
Maxima Medisch Centrum

De Run 4600
Veldhoven 5504 DB
NL
Scientific
Maxima Medisch Centrum

De Run 4600
Veldhoven 5504 DB
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Inclusion of subjects in the IRIDA group will take place from a population earlier studied by Donker et al, for these subjects clinical data are already available. (Donker et al, Am J Hematol 2016), Inclusion of subjects in the non-IRIDA, iron deficiency anemia group will take place at the gynaecological department (women suffering from menorrhagia) and at the gastrointestinal department (gastrointestinal blood loss and/or malabsorption), the cardiology department, the ER of the Maxima Medical Center
IRIDA group
In order to be included in this study an IRIDA patient should meet the following criteria:
- Previous diagnosis as a mono-allelic or bi-allelic IRIDA patient with an IRIDA phenotype detected after clinical presentation
- Presence of microcytic anemia (MCV < 80 fL and Hb <7.5 mmol/L for women, Hb < 8.5 mmol/L for men)
- Transferrin saturation (TSAT) < 10%
- Absence of inflammation (CRP < 10 mg/L)
- Not or partially responsive to oral iron (responsiveness to oral iron defined as Hb increment of 2 g/dL after 3 weeks of iron therapy)
- Age above 18 years
-TSAT/hepcidin ratio available, determined in the absence of inflammation,
Based on these criteria 4 patients in a population of 21 will be excluded because either the patient was < 18 years or the TSAT/hepcidin ratio was not available, or not available in the absence of inflammation.
The other 17 IRIDA patients will be included in the study; 11 IRIDA patients in the bi-allelic affected group, with a homozygous or a compound heterozygous TMPRSS6 defect, and 6 subjects in the mono-allelic affected group with a heterozygous TMPRSS6 defect., Control group, Because the controls in the SATURNUS study all have a microcytic anemia comparable with the IRIDA group, the phenotype is not discriminative. Therefore, in all controls genotyping of

the exons of TMPRSS6 will be performed. A relevant phenotype, see below, in combination with the absence of pathological TMPRSS6 variants on both alleles will be defined as non-IRIDA and will be eligible as control. , Inclusion of subjects in the control group will take place at the above mentioned departments of the Máxima Medical Centrum Veldhoven and Radboudumc Nijmegen. In order to be eligible to participate in this study a subject should meet the following criteria:
o Presence of microcytic anemia (MCV <80 fL and Hb <7.5 mmol/L L for women, Hb < 8.5 mmol/L for men)
o Ferritin <40 µg/L
o Age >18 years
o Low TSAT (TSAT <10%)
o Absence of inflammation (CRP < 10 mg/L)
o Absence of pathological TMPRSS6 variants in exons of both alleles, - After counselling of a potential eligible patient by the Emergency Room doctor, the cardiologist, the gastro-intestinal specialist or the gynaecologist, blood is withdrawn for the determination of Hb, MCV, ferritin and CRP level. Extra blood is withdrawn and stored for the determination of hepcidin and for DNA studies on TMPRSS6 defects in case the subject had indeed an iron deficiency anemia without inflammation and has given informed consent. In case the subject does not meet the inclusion criteria or does not give informed consent, this extra material will be destroyed.

Exclusion criteria

IRIDA group: see above, D4a, inclusions already done, Control group
Subjects with the following criteria will not be able to participate in the study because these criteria interfere with the TSAT and hepcidin values.
- Pregnancy
- Oral iron supplements in the last 3 months before referral to the gynaecologist or gastrointestinal specialist
- Diagnosis with any disease associated with inflammation including malignancies, chronic liver and kidney diseases

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Diagnostic

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	07-02-2018
Enrollment:	94
Type:	Actual

Ethics review

Approved WMO Date:	19-09-2017
Application type:	First submission
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	16-02-2018
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	13-06-2018
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	16-01-2019
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)
Approved WMO Date:	27-01-2020
Application type:	Amendment
Review commission:	METC Maxima Medisch Centrum (Veldhoven)

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	NL61876.015.17