Investigating the interplay between iron (overload) and erythropoiesis in rare hereditary anemias.

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Investigate regulators of (disturbed) iron homeostasis and cellular determinants of iron overload in RHA. to decipher crucial elements of the crosstalk between iron metabolism and erythropoiesis

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Red blood cell disorders
Study type	Observational invasive

Summary

ID

NL-OMON49379

Source
ToetsingOnline

Brief title
Effects of iron overload on erythropoiesis

Condition

- Red blood cell disorders

Synonym
congenital anemia, rare hereditary anemia

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Erythropiesis, Iron overload, Rare hereditary anemia

Outcome measures

Primary outcome

• To investigate key-regulators and cellular determinants of iron overload in RHA

• To investigate the role of ferroptosis in ineffective erythropoiesis, RBC survival and RBC maturation in RHA.

Secondary outcome

• To investigate whether metabolomics can be used to study distinct and shared defects in iron homeostasis in rare hereditary anemias.

• To investigate whether targeting hepcidin and/or ferroptosis can improve erythropoiesis and RBC defects.

Study description

Background summary

The group of rare hereditary anemias (RHA) includes a large variety of defects of red blood cells and erythropoiesis, including hemoglobinopathies, erythrocyte enzyme defects and hypoplastic anemias, such as Diamond Blackfan anemia (DBA). Despite very disease-specific manifestations, this group of disorders also shares important clinical, hematological and biochemical features, including ineffective erythropoiesis, and disturbed iron homeostasis. In RHA, iron overload is a common and severe complication, inducing severe organ damage, including liver fibrosis, heart failure, and endocrine dysfunction. In addition, iron excess induces reactive oxygen species (ROS)-mediated toxicity to bone marrow stromal cells, further worsening the effects of chronic anemia. Surprisingly, whereas the regulation of iron homeostasis is obviously crucial for patients with severe chronic anemias and iron overload, there is still little understanding concerning disease-specific regulators of iron homeostasis and their role in ineffective erythropoiesis.

Mechanisms that have been suggested include differential regulation of reactive oxygen species (ROS), and more recently, ferroptosis, an alternative form of regulated cell death, characterized by the accumulation of lipid peroxidation products and lethal ROS, and functionally directly linked to iron metabolism. Together, it seems conceivable that manipulation of the hepcidin pathway (regulating iron uptake and recycling), and targeting ferroptosis in RHA could improve iron hemostasis and consequently erythropoiesis. In order to investigate this and to increase our understanding of the functional interplay between iron and erythropoiesis in RHA, a novel explorative approach is needed.

Study objective

Investigate regulators of (disturbed) iron homeostasis and cellular determinants of iron overload in RHA. to decipher crucial elements of the crosstalk between iron metabolism and erythropoiesis

Study design

This study is a longitudinal observational study in which in vitro assays will be performed on peripheral blood samples (and stored bone marrow samples) collected at routine visits at the outpatients* clinic.

Study burden and risks

Burden: In this study we will collect additional blood samples for in vitro studies. Therefore, the burden will be minimal.
There will be no interventions as the collection of blood for this study will be combined with routine venipunctures during their visit to the outpatient clinic. This implicates there will also be no additional risks.

Benefit: The clinical consequences of chronic anemia and iron overload are important issues during long term clinical management of patients with RHA. Therefore, a better understanding of the mechanisms driving disturbed iron homeostasis, and the effects on erythropoiesis are crucial. This study will contribute to the identification of novel therapeutic targets to improve our clinical management of iron overload and ineffective erythropoiesis in RHA.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (12-15 years)
Adolescents (16-17 years)
Adults (18-64 years)
Children (2-11 years)
Elderly (65 years and older)

Inclusion criteria

• Age > 12months
• No blood transfusion within the past 4 weeks
• Diagnosed with rare hereditary anemie, including sickle cell anemia, betathalassemia,
spherocytosis, xerocytosis, pyruvate kinase deficiency (and other enzyme defects)
Diamond- Blackfan Anemia, Congenital Dyserythropoietic Anemia.
• Parents/legal guardians (and child, depending on age) or adult patients have given written
informed consent

Exclusion criteria

• Age < 12 months
• Body weight below 10 kg

• Blood transfusion within past 4 weeks

Study design

Design

Study type: Observational invasive

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	10-02-2021
Enrollment:	50
Type:	Actual

Ethics review

Approved WMO

Date:	07-10-2020
Application type:	First submission
Review commission:	METC NedMec

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	NL73462.041.20