# Disturbed ion homeostasis in hereditary hemolytic anaemia

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Primary objectives:(i) To study the pathophysiology, in particular the role of disturbed ion channel function in hereditary haemolytic anaemia(ii) To define novel intra- and extracellular (bio)markers in hereditary haemolytic anaemia. Secondary...

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| **Ethical review** | Approved WMO |
| **Status** | Recruitment stopped |
| **Health condition type** | Red blood cell disorders |
| **Study type** | Observational invasive |

## Summary

### ID

NL-OMON43679

**Source**
ToetsingOnline

**Brief title**
Ion homeostasis in rare anaemia

### Condition

- Red blood cell disorders

**Synonym**
bloedarmoede, heriditary hemolytic anaemia

**Research involving**
Human

### Sponsors and support

**Primary sponsor:** Universitair Medisch Centrum Utrecht
**Source(s) of monetary or material Support:** Europese Unie (this project has received funding from the European Union□s Seventh Framework Programme for research;technological development and demonstration under grant agreement No 602121)

## Intervention

**Keyword:** erythrocytes, ion channels, ion homeostasis, microvesicles

## Outcome measures

### Primary outcome

o Routine red blood cell characteristics (cytology)

o Red blood cell morphology

o Routine chemistry analysis; iron, ferritin, transferrin, vitamin B12, serum folate and haptopglobin levels

o Eosin-5-maleimide (EMA) binding on surface of red blood cells

o Osmotic fragility

o Osmotic gradient ektacytometry (LoRRca MaxSis)

o Deformability (LoRRca MaxSis)

o Intracellular Na+ and K+ levels

o Flow cytometric analysis of red blood cells: phosphatidyl serine exposure, CD47, band3, CD71, CD235a, intracellular Ca2+

o Glutathione measurement: ratio between GSH/GSSG

o Surface protein expression of RBC microvesicles

o Quantity and size distribution of RBC microvesicles

o Conductance and patch-clamp measurements of red blood cells

o Calcium homeostasis after chemical stimulation of red blood cells

o Hemoglobin oxygen affinity

o Red blood cell density; Percoll and filtration

o ATP levels

o DNA analysis (Next Generation Sequencing)

**Secondary outcome**

o Development of an optical sorting device with scanning ion conductance microscope (end points: (1) percentage sorted and/or percentage of interesting red cells based on morphology and/or fluorescent probes and (2) symmetry of (sorted) red cells measured with SICM).

# Study description

**Background summary**

Anaemia in general, is defined as a haemoglobin concentration less than 6,8 - 8,0 mmol/L depending on gender and age. It affects 1.6 billion individuals worldwide.

Approximately 10% of these individuals are affected by rare anaemia. This disease group includes approximately 90 different types of red blood cell (RBC) diseases, of which 80% are hereditary or congenital in nature. Hereditary haemolytic anaemia (HHA) constitutes an important subgroup of rare anaemias, and is characterized by decreased red blood cell survival. As the pathophysiology of the majority of rare anaemias is poorly understood, appropriate treatment is often ineffective or even lacking. Although the total number of affected individuals is substantial, the diversity in the underlying causes has resulted in limited interest from the pharmaceutical industry.

Recent studies indicate that some forms of HHA are associated with altered cellular ion homeostasis. Primary and secondary causes can be distinguished. In primary causes defective function of the ion channel directly causes the disease. Examples include hereditary xerocytosis, overhydrated hereditary stomatocytosis, familial pseudohyperkalaemia, cryohydrocytosis and certain types of spherocytosis.
Secondary causes are due to other structural and hereditary RBC abnormalities. Examples are hereditary spherocytosis, haemoglobinopathies (e.g., sickle cell anaemia, thalassemia and glucose transporter GLUT1 mutations. Moreover, enzymes deficiencies (e.g., phosphofructokinase deficiency) may also be associated with altered cellular ion homeostasis.

It also appears reasonable to assume that disturbed ion homeostasis may significantly contribute to anaemia pathophysiology and, in addition, may

constitute an important group of undiagnosed cases of HHA.

### Study objective

Primary objectives:
(i) To study the pathophysiology, in particular the role of disturbed ion channel function in hereditary haemolytic anaemia
(ii) To define novel intra- and extracellular (bio)markers in hereditary haemolytic anaemia.

Secondary objective:
To develop new diagnostic tools for yet undiscovered forms of hereditary haemolytic anaemia

### Study design

The proposed study is a mono-center descriptive cohort study.

In this study patients with known and unknown causes for hereditary haemolytic anaemia will be recruited by the University Medical Centre Utrecht (Utrecht, The Netherlands).

### Study burden and risks

Burden is limitid to the donation of 42 ml of blood by venapuncture. Burden from parents of patients suffering from hereditary hemolytic anaemia e.c.i.

## Contacts

**Public**
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL
**Scientific**
Universitair Medisch Centrum Utrecht

Heidelberglaan 100
Utrecht 3584CX
NL

# 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

Patient suffering from HHA, based on the following criteria;
• A proposed RBC ion homeostasis disturbance due to a primary cause; membrane defects (spherocytosis, stomatocytosis) of the red blood cell (previously diagnosed by with a decreased EImax detected by osmotic gradient ektacytometry, or altered osmotic fragility, or altered EMA-binding test, or mutations found in SPTA1, SPTB, SLC4A1, ANK1, EPB41, EPB42, PIEZO1, RHAG.
• A proposed RBC ion homeostasis disturbance due to a secondary cause; hemoglobinopathies (sickle cell anaemia, thallasemia) or enzymopathies of the red cell (previously diagnosed by detection of HbA2, HbF, HbS, HbE, HbD, HbC by electrophoresis, or decreased enzyme activity in red blood cell enzymes (PK, HK, G6PD, GPI, F-ALD, TPI, PGK, BPGM, GSR), or mutations found in HBA1, HBA2, HBB, PFKM, PGK1, G6PD, GPI1, HK1, PKLR)
• Hemolytic anemia due to an unknown cause; patients previously screened for iron deficiency anaemia and other forms of nutritional deficiency anaemia, anaemia due to chronic illnesses or infection, membrane defects of the red cell, hemoglobinopathies and/or enzymopathies, without the detection of a (molecular) cause for the haemolytic anaemia.
- Biological parent of a patient suffering from haemolytic anaemia due to an unknown cause

## Exclusion criteria

- Transfusion (erythrocyte concentrate) received in the last 90 days
- For children: body weight <= 18kg
- Age <= 3 years

# Study design

## Design

**Study type:** Observational invasive

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|---|---|
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Diagnostic |

## Recruitment

NL

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|---|---|
| Recruitment status: | Recruitment stopped |
| Start date (anticipated): | 21-12-2015 |
| Enrollment: | 140 |
| Type: | Actual |

# Ethics review

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| Approved WMO Date: | 21-10-2015 |
| Application type: | First submission |
| Review commission: | METC NedMec |
| Approved WMO Date: | 17-03-2016 |
| Application type: | Amendment |
| 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 | NL54017.041.15 |

# Study results