The pathogenesis of dengue virus infection in patients with sickle cell disease

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To elucidate the pathogenetic mechanism of endothelial cell activation in DENV infected patients with sickle cell disorder.

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Haemoglobinopathies
Study type	Observational invasive

Summary

ID

NL-OMON37382

Source
ToetsingOnline

Brief title
Dengue virus infection and sickle cell disease

Condition

- Haemoglobinopathies
- Viral infectious disorders

Synonym
break-bone fever, dengue

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Dengue virus, Endothelium, Sickle cell disease

Outcome measures

Primary outcome

From the supernatant of the HUVECs which were incubated with the DENV infected

PBMCs we would like to investigate the following parameters:

Virus titre

Inflammatory markers (TNF-α, IL-1β)

Coagulation markers(TF, sTM)

Secondary outcome

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Study description

Background summary

Annually an estimated number of 50 - 100 million dengue virus (DENV) infections occur in tropical and subtropical countries around the world. DENV-infection usually results in a subclinical or self-limiting febrile disease but may also lead to severe disease, previously known as Dengue haemorrhagic fever (DHF) and Dengue shock syndrome (DSS). Severe disease is characterised by thrombocytopenia, haemorrhagic manifestations, liver disturbances and a sudden onset of vascular permeability, believed to be caused by a cytokine storm.

Important clinical symptoms of severe DENV infection are plasma leakage and bleeding. It is believed that both symptoms are partially caused by activation of endothelial cells. However, the primary target cells of DENV infection are monocytes. It has been shown that endothelial cells can be infected with DENV in vitro, but whether viral replication in endothelial cells really happens in vivo is still a matter of debate.

A fatal case of a DENV infected patient with sickle cell disease celled to the hypothesis that sickle anaemia may worsen the clinical course of a DENV infection. During an outbreak in Cuba, a relationship between sickle cell

anaemia and severe DENV infections has been described. It was hypothesized that the monocytes of patients with sickle cells disease have a lower inflammatory set-point, which leads to activation of endothelial cells. Since endothelial cells in patients with sickle cell disorder are activated without any concurrent infection, it is conceivable that hyper-reactivity of macrophages during DENV infection in these patients amplifies the activational status of endothelial cells, leading to severe plasma leakage and bleeding.

Study objective

To elucidate the pathogenetic mechanism of endothelial cell activation in DENV infected patients with sickle cell disorder.

Study design

Experimental in vitro study with human-derived material

Patients visiting the out-patient clinic of the department of hematology (only adults) of internal medicine will be asked to participate in this study. After informed consent is obtained blood will be drawn via venipuncture.

The following specimens will be collected:
EDTA blood (20cc) in order to isolate PBMCs

Materials/methods
Peripheral blood will be drawn in 2 X 10 mL EDTA tubes. Samples will be kept at 40C and be processed immediately. The PBMCs will be separated from the other blood fraction with a Ficoll layer. To set a baseline the PBMCs of patients with HbSS and of healthy controls will be stimulated with LPS and conA to investigate whether the inflammatory setpoint of PBMCs from patients with sickle cell disease is indeed increased. Afterwards the PBMCs will be infected with dengue virus and incubated with Human Umbilical Vein Endothelial Cells for approximately 5-7 days. Every day samples from the supernatant will be taken and the virus titre and certain coagulation (TF, sTM) and inflammatory parameters (TNF-α, IL-1β) will be measured.

Study burden and risks

There may be a risk for pain and/or a hematoma at the venipuncture site.

Contacts

Public
Erasmus MC, Universitair Medisch Centrum Rotterdam

postbus 2040
3000 CA Rotterdam
NL
Scientific
Erasmus MC, Universitair Medisch Centrum Rotterdam

postbus 2040
3000 CA Rotterdam
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Adult patient with sickle cell disease (HbSS genotype)

Exclusion criteria

Blood transfusion in the preceding three months.
Painful vaso-occlusive crisis/acute chest syndrome/stroke or other acute complications in the preceding 2 weeks.
Current use of hydroxyurea.

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)
Control:	Active
Primary purpose:	Basic science

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	24-05-2012
Enrollment:	26
Type:	Actual

Ethics review

Approved WMO

Date:	20-03-2012
Application type:	First submission
Review commission:	METC Erasmus MC, Universitair Medisch Centrum Rotterdam (Rotterdam)

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	NL39271.078.11