The role of the immune system in Q Fever Fatigue Syndrome

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Ethical review	Approved WMO
Status	Recruiting
Health condition type	Ancillary infectious topics
Study type	Observational invasive

Summary

ID

NL-OMON42442

Source
ToetsingOnline

Brief title
QFS - Immunopathology

Condition

- Ancillary infectious topics

Synonym
Coxiella burnetii, Q fever

Research involving
Human

Sponsors and support

Primary sponsor: Stichting Q-support (verlenen subsidie)
Source(s) of monetary or material Support: Stichting Q-support (verlenen subsidie;is GEEN opdracht)

Intervention

Keyword: Fatigue, Immunopathology, Q fever, QFS

Outcome measures

Primary outcome

Primary outcome measures:

•Cytokine concentrations (IL-6, IL-8, IL-10, IFN-γ and TNF-α)

•Epigenetic changes in the different groups of patients (histone modification H3K4me3).

•Transcriptome analysis

Cytokine concentrations will be measured with ELISA kits while epigenetic changes will be measured with chromatine immunoprecipitation. Transcriptome analysis will be conducted through RNA sequencing and biostatic pathway analysis.

Secondary outcome

Not applicable.

Study description

Background summary

Q Fever Fatigue Syndrome (QFS) is a well documented state of prolonged fatigue, following acute Q fever. Up to 20% of patients that are diagnosed with acute Q fever will develop QFS, leading to a substantial burden for the affected patients. This burden constitutes the morbidity, socio-economic weight and consequences of the disease. Current research focuses mainly on new methods for diagnosing and treating QFS, while the questions as to why people with QFS stay fatigued remain unanswered. We would like to investigate the hypothesis that Coxiella Burnetii (the bacteria that causes Q fever) is able to elicit

epigenetic changes in the monocytes and macrophages that try to clear it. These epigenetic changes could trigger the cells in such a way that they will secrete higher levels of pro-inflammatory cytokines, ultimately resulting in a state of prolonged fatigue (QFS).

Study objective

This study will try to objectify if C. Burnetii is able to induce epigenetic changes in monocytes and macrophages, ultimately resulting in a changed cytokine profile. Subsequently, this study will try to link these epigenetic changes to mRNA expression in the blood of patients and controls.

Study design

An observational case-control study will be performed to determine whether C. Burnetii is able to induce epigenetic changes in monocytes and macrophages, ultimately altering their cytokine production. This study will consist of two main approaches:
•In-vitro experiments will be conducted on Peripheral Blood Mononuclear Cells (PBMCs) derived from buffy coats of healthy volunteers. PBMCs will be pre-incubated with C. Burnetii, after which they will be stimulated with different Pathway Recognition Receptor (PRR) ligands, C. Burnetii or other bacteria. Once PBMCs are re-stimulated, concentrations of IL-6, IL-8, IL-10 and TNF-α (cytokines) will be measured in the supernatants and the histone modification H3K4me3 (related to epigenetic changes) will be investigated through chromatine immunoprecipitation and qPCR.

•In-vitro experiments will be conducted on blood derived from QFS patients, Chronic Fatigue Syndrome (CFS) patients, patients with a past C. Burnetii infection without QFS and healthy controls. PBMC*s will be isolated and subsequently stimulated with C. burnetii, other bacteria and PRR ligands. After stimulation, pro-inflammatory cytokine responses (IL-6, TNF- α and IFN-γ) will be measured. This will give us a preliminary idea of the amount of trained monocytes in different groups. As soon as this data is analyzed, transcriptome analysis of leucocytes will be performed in order to link the histone modifications that might have been found in the former experiment, to mRNA expression in-vivo.

After informed consent has been obtained, blood will be drawn in 4 EDTA tubes of 10 ml. RNA of set leucocytes will be stabilized and stored in a freezer until the RNA can be isolated. RNA sequencing will be done after RNA isolation and library preparation has been performed according to standard protocols of the BLUEPRINT-epigenome project and illumine library preparation protocol.

The duration of this study is 2 year. Patients and controls will be recruited from the Radboudumc and collaborating hospitals.

Study burden and risks

Burden:
•For patients: collection of extra blood, if possible during regular blood sampling (for CFS and QFS patients), in the form of 4 EDTA tubes of 10 ml
•For controls: the same as for patients, blood samples will only be used for the research purposes that are described in this study

Risk:
•No risks other than local hematoma are related to venous puncture

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

Q Fever Fatigue Syndrome (QFS):
•Diagnosis of QFS according to national LCI-guideline Q fever fatigue syndrome (QFS)
•Score >=40 on the subschale fatigue of the Checklist Individual Strength (CIS)
•Severe functional impairment on Sickness Impact Profile-8 (SIP-8), defined as a SIP total score >=700
•Age >=18;Chronic Fatigue Syndrome (CFS):
•Diagnosed with CFS according to CDC-criteria (www.cdc.gov/cfs)
•Score >=40 on the subschale fatigue of the CIS
•Severe functional impairment on Sickness Impact Profile-8 (SIP-8), defined as a SIP total score >=700
•Age >=18;Cleared acute Q fever without residual symptoms:
•Cleared acute Q fever (without residual symptoms)
•Age >=18;Healthy serologic negative volunteers:
•Negative Q fever serology as tested by immunofluorescence assay (IFA)
•Age >=18

Exclusion criteria

Q Fever Fatigue Syndrome (QFS):
•Use of immunosuppressant drugs during an acute Q fever infection or in the past 3 months
•Pregnancy
•Use of antibiotics that are potentially active against C. Burnetii for at least 4 weeks, after the diagnosis acute Q fever was made;Chronic Fatigue Syndrome (CFS):
•Use of immunosuppressant drugs in the past 3 months
•History of Q fever
•Chronic Q fever patients, according to the Dutch consensus *Chronic Q fever*
•Vaccinated for Q fever
•Pregnancy;Cleared acute Q fever without residual symptoms:
•Use of immunosuppressant drugs during an acute Q fever infection or in the past 3 months
•Chronic Q fever patients, according to the national consensus *Chronic Q fever* [RIVM, Q-koortsvermoeidheidssyndroom]
•Vaccinated for Q fever
•QFS or CFS
•Evident somatic or psychiatric morbidity
•Pregnancy ;Healthy serologic negative volunteers:
•Use of immunosuppressant drugs in the past 3 months
•History of Q fever
•Chronic Q fever patients, according to the national consensus *Chronische Q-koorts*
•Vaccinated for Q fever
•QFS or CFS
•Evident somatic or psychiatric morbidity
•Pregnancy

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):	30-11-2015
Enrollment:	80
Type:	Actual

Ethics review

Approved WMO Date:	02-06-2015
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

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	NL52893.091.15