500NL project

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The aim of the study is to test the hypothesis that susceptibility to and severity of certain infectious and inflammatory diseases can be explained by the interaction between the genome, microbiome and immunological responses: i.e. presence of...

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Observational invasive

Summary

ID

NL-OMON37251

Source
ToetsingOnline

Brief title
500NL

Condition

- Other condition
- Immunodeficiency syndromes
- Hepatobiliary neoplasms malignant and unspecified

Synonym
Infectious diseases and autoimmune diseases

Health condition

Autoimmuunziekten

Research involving
Human

Sponsors and support

Primary sponsor: Universitair Medisch Centrum Sint Radboud
Source(s) of monetary or material Support: ERC Consolidator Grant

Intervention

Keyword: Immunology, Metabolomics, Microbiome, Transcriptomics

Outcome measures

Primary outcome

Metadata: Lifestyle questionnaires

DNA: Gene polymorphisms at DNA level

Microbiome: Presence of groups of bacteria

Phenotype: Specific populations of cells

Functional data: Cytokine production

Secondary outcome

Niet van toepassing

Study description

Background summary

Several factors have been demonstrated to date to have a crucial effect on the susceptibility and outcome of infections and (auto)inflammatory diseases: (1) the genetic make-up of the individual, (2) the colonizing microorganisms on its skin and mucosae, and (3) variations in the immune responses.

(1) The knowledge about DNA polymorphisms has become a valuable parameter for assessing risks to develop many important human diseases. Recently, we (and others) have demonstrated that polymorphisms in immunity-related genes lead to differences in susceptibility to fungal diseases (1), bacterial infections such as Borrelia or Bacteroides (2, 3), arthritis (4), or autoimmune disorders such as inflammatory bowel disease of Crohn*s disease (5, 6).

(2) Next to differences in DNA patterns, it could also be demonstrated that the

presence of certain microorganisms in the gut (e.g. probiotic bacteria) are able to influence the cytokine production and possible the clinical outcome (7, 8). All vertebrates display complex communities of microorganisms on body surfaces, called the microbiome or microbiota. However, most of these microbes are not cultivable and therefore 16S sequence analysis has proven to give crucial information regarding the complexity of microbial communities on the skin and mucosae (9). The knowledge about the variation in the human gut will be increased in a second project called the Human Microbiome project (10). A search on PubMed indicates the exponential growth of this discipline (0 in 1999 against 865 articles in 2011). The microbiome was demonstrated to give valuable information about the origin, lifestyle, development of immune responses, infections, metabolic and autoimmune diseases (11). Next to microbial patterns in the gut, urine and skin samples were also described to give valuable information in health and disease (12, 13). It could be demonstrated that the microbial components present in the human body can be related to immune responses or autoinflammatory disorders (14, 15). Therefore, it is plausible to link the differences in microbial status and illnesses (16).

(3) Next to the presence or absence of certain groups of microbes in disease, the phenotype and function of circulating cells might also differ between health and disease. In HIV/AIDS patients is the best example described, a typical mark of this disease is decreased CD4+ T cell circulation. Next to HIV/AIDS, CD4+ T cells were also described to differ in certain stages of tuberculosis (17), arthritis (18) and Crohn*s disease (19). Next to T cells, other cell types, such as dendritic cells, may also change their phenotypic characteristics during disease (20).
The capacity of immune cells to produce cytokines and chemokines has proven to be highly important in health and disease. Differences in cytokine production were linked to several diseases, including Lyme disease (2), Crohn*s disease (6), but also fungal infections with for example candida (21). Individuals with altered cytokine responses were reported to be highly susceptible for the development of disease.

Despite the research that has linked each of these processes to the susceptibility to disease, practically nothing is known how they influence each other and how does this interaction relate to the various diseases. In other words, it is not known whether genetic polymorphisms influence the composition of the microbiome, how these two factors together modify the immune response of the host, and what are the consequences for the susceptibility to infections or (auto)inflammatory disorders. This is the aim of the recently awarded ERC-Consolidator Grant (nr.310372) to M.G. Netea, that stays at the core of this study.

Therefore, we will assess by systems biology and pathway analysis the interaction between the DNA polymorphisms on the one hand, the microbiome of the skin, intestinal tract and vagina, and the immune responses in a large group of healthy individuals. After assessing the interaction of these factors

in healthy controls, we will assess whether this balance is distorted in certain patients groups with infections or (auto)inflammatory disorders.

Study objective

The aim of the study is to test the hypothesis that susceptibility to and severity of certain infectious and inflammatory diseases can be explained by the interaction between the genome, microbiome and immunological responses: i.e. presence of polymorphisms, differences in microbial composition, differences in phenotypes and/or of circulating cells (altered cytokine production).

Specific research questions are:
1. Do genetic variations influence the immune responses and subsequently the susceptibility or severity of disease?
2. Is there a difference in the composition of the microbiome between healthy and patient groups?
3. Is the colonization with certain classes of microorganisms influenced by genetic polymorphisms of the host?
4. What is the phenotype and function of the circulating cells in patients and controls, and is that influenced by the gene polymorphisms on the one hand, and microbiome on the other hand?

Study design

The study comprises a case-control study. The duration of the study is 3 years and will be performed in the Radboud University Nijmegen Medical Centre (RUNMC), in collaboration with Harvard School of Medicine and UMC Groningen. Patients will be recruited from the RUNMC.

Study burden and risks

Burden:
- For patients and controls: collection of venous blood, if possible during regular blood sampling. This comprises a maximum of 1 heparin tube à 10 ml, 1 PaxGene tube a 8 mL, 1 citrate tube a 3 mL and 6 EDTA tubes à 10 ml and 1 serum tube à 5 ml.
- For controls: the same as for patients, but blood sampling for the purpose of this study only will be necessary in all cases.

Risks:
- No risks other than local hematoma are related to venous puncture.

Benefit:
There will be no benefits for the subjects enrolled in this study.

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

healthy volunteers (n=500):
- older than 18 years
- no chronic or acute disease at the time of assessment
- no use of chronic or acute medication at the time of the study
Inclusion criteria for the patient groups:;RVVC patients (n=200)
- healthy women, age >18 years
- no pregnancy, no diabetes, no antibiotic use
- at least 3 episodes of vulvo-vaginal candidiasis per year, microbiologically confirmed;Candidemia patients (n=50)
- patient with blood culture positive for a Candida species
- age > 18 years
- treatment given no longer than 24h before sample collection;Lyme disease patients

(n=150)
- age > 18 years old
- clinical diagnosis based on erythema migrans.
- positive serology (IgG) for Borrelia. ;Gout patients (n=200)
- age > 18 years
- diagnosis based on clinical criteria and positive urate crystals in the joint fluid;HIV-infected patients (n=400)
- age > 18 years
- HIV infection based on viral loads and CD4 counts
- no opportunistic infection at the time of sampling

Exclusion criteria

Pregancy
Age<18 years

Study design

Design

Study type:	Observational invasive
Intervention model:	Other
Allocation:	Non-randomized controlled trial
Masking:	Open (masking not used)

Primary purpose: Other

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	01-08-2013
Enrollment:	1500
Type:	Actual

Ethics review

Approved WMO

Date:	01-05-2013

Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-05-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	29-09-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	19-11-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	10-05-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	06-09-2016
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	17-07-2017
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	16-07-2018
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	NL42561.091.12