MeninGene Recall study, substudy of the MeninGene study

Published: 30-07-2015
Last updated: 19-04-2024

1. Characterize the interplay between host factors and bacterial factors and the specific activation of inflammatory pathways.2. Evaluate the expression of identified risk genes after activation of inflammatory pathways in host immune mediating...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Bacterial infectious disorders
Study type	Observational invasive

Summary

ID

NL-OMON42352

Source
ToetsingOnline

Brief title
MeninGene Recall study

Condition

- Bacterial infectious disorders
- Central nervous system infections and inflammations

Synonym
bacterial meningitis

Research involving
Human

Sponsors and support

Primary sponsor: Academisch Medisch Centrum
Source(s) of monetary or material Support: NWO Vidi beurs. D. van de Beek;Veni beurs M.C. Brouwer,ERC starting grant D. van de Beek

Intervention

Keyword: Follow-up, Genexpression, Meningitis

Outcome measures

Primary outcome

- Baseline activity of the immune system and activation of the immune system

assessed by ex vivo stimulation experiments

- Cognitive functioning

Secondary outcome

- Quality of life

- Quality of sleep

- Antibody titers

Study description

Background summary

Bacterial meningitis is a life-threatening disease.1 The estimated incidence is 2-5 per 100.000 people per year in developed countries and is up to ten-times higher in resource poor countries.1-4 The most common causative bacteria is the Streptococcus pneumonia in 70% of the cases. 1,2 Despite treatment with antibiotics and dexamethasone the mortality and morbidity is still high. Especially in pneumococcal meningitis the fatality rate is substantial (26%).1,2

Understanding host genetic factors by PBMC and whole blood stimulation
Bacterial meningitis is a complex disorder in which injury is caused, in part, by the causative organism and, in part, by the host*s own inflammatory response.5 Both host and bacterial genetic factors influence this process.6-8 Further characterisation of the interplay between host and bacterial factors is needed to increase our understanding in the pathophysiology of bacterial meningitis.
Genetic variations influencing susceptibility and severity of bacterial meningitis are identified in genes coding for the immune system.8,10-12 To enhance understanding of the functionality of these genetic variations stimulated peripheral blood mononuclear cells (PBMCs) and whole blood can be

used to study the immune response.9 After stimulation of PBMCs and whole blood with bacteria or pathogen-associated molecular patterns activation of the immune response can be analysed by measuring cytokine production and mRNA expression.9
Our hypothesis is that differences in the immune response activation will be found when stimulating PBMCs and whole blood of survivors of bacterial meningitis with different genetic profiles. The activation of the immune system will be compared between individuals with risk genotypes and those with protective genotypes. Also differences in the immune response activation between survivors of bacterial meningitis and healthy controls will be compared. Determination of differences in immune activation will give us more insight in the pathophysiology of bacterial meningitis and will help us to find new targets for prevention or treatment.

Long term effects of bacterial meningitis
In survivors of bacterial meningitis neurological and neuropsychological sequelae occur frequently. Even in patients with a good recovery, cognitive impairments are common and affect one third of patients with pneumococcal and meningococcal meningitis.13 The affected cognitive domains differ between studies, but a study with pooled data showed most of cognitive impairments were associated with a decline in cognitive speed.13-16 Despite concerns about possible harmful effects of adjunctive dexamethasone therapy on cognition, earlier studies did not pointed out an association between dexamethasone and cognitive impairments in bacterial meningitis patients.16 Nowadays dexamethasone is a routine therapy in adults with bacterial meningitis, therefore evaluation of the long term affect on cognitive functioning is still important.
Another long term finding in bacterial meningitis patients is a decreased quality of sleep. Sleep disturbance is common in survivors of meningitis (58%), but the pathophysiological understanding is still unknown.17 Possibly, structural brain lesions due to the inflammatory disease underlie sleep disturbances in meningitis patients. Still, large patient groups in order to assess the extent and frequency of sleep disorders in bacterial (and in particular pneumococcal) meningitis are lacking. In this study we will assess quality of sleep and screen for possible related depressive mood disorders in patients and controls.
Furthermore we will determine pituitary hormone function in survivors of bacterial meningitis and healthy controls. Various case reports and retrospective studies suggest bacterial meningitis is a frequent cause of pituitary dysfunction, but larger patient cohorts are lacking.18 Since hormone dysfunction could be clinically important, we want to assess the long term pituitary function in survivors of bacterial meningitis. In order to assess clinical relevance of possible findings we will investigate correlations between hormonal function and quality of sleep.

Adaptive immune system after bacterial meningitis
The innate immune system plays an important role in bacterial meningitis, but

the role of the adaptive immune system is still unclear. In this study, we want to sequence gene expression of B cells in search for long term memory signals that are unique to survivors of bacterial meningitis. Furthermore we will measure pneumococcal and anti-neuronal antibodies to determine if an adequate immune response did take place and patients did acquired long term protection for new pneumococcal infections.

Study objective

1. Characterize the interplay between host factors and bacterial factors and the specific activation of inflammatory pathways.
2. Evaluate the expression of identified risk genes after activation of inflammatory pathways in host immune mediating cells.
3. Determine differences in expression of immune genes in survivors of bacterial meningitis and healthy controls.
4. Determine the long term effects of bacterial meningitis on quality of life, quality of sleep and cognitive functioning
5. Evaluate pneumococcal and anti-neuronal antibody titers and expression patterns in B cells of survivors of bacterial meningitis

Study design

In the MeninGene study, patient DNA was analyzed for genetic variations that influence susceptibility and severity of disease. In this sub-study effects of those genetic variations on the immune response are studied by stimulation experiments. Furthermore, blood samples will be used to analyze baseline activity of the immune system (cytokine, chemokine, complement and antibody levels), hormone function and to isolate B cells to assess the B-cell repertoire. After the blood withdrawal patients will have a neurological examination, fill in questionnaires and perform a neuropsychological assessment.

Study burden and risks

A single blood withdrawal of maximum 100 cc will be performed in each participant. Risks of a blood withdrawal are negligible. Filling in the questionnaires will take less than 30 minutes. The cognitive functioning will be assessed with an online assessment taking one hour.

Contacts

Public
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL
Scientific
Academisch Medisch Centrum

Meibergdreef 9
Amsterdam 1105 AZ
NL

Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

Adult survivors of community acquired bacterial meningitis who:
1. Participated in the Dutch Bacterial Meningitis Study II or MeninGene study
2. Gave informed consent to be approached for new research projects;Control persons who:
1. Participated in the Dutch Bacterial Meningitis Study II or MeninGene study
2. Gave informed consent to be approached for new research projects

Exclusion criteria

Patients en control persons who:
Had a bacterial meningitis episode in the 6 months previous to participation

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):	08-10-2015
Enrollment:	300
Type:	Actual

Ethics review

Approved WMO

Date:	30-07-2015
Application type:	First submission
Review commission:	METC Amsterdam UMC

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	NL54045.018.15