Nationwide prospective study on community-acquired bacterial meningitis: from genetics to therapy

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

Summary

ID

NL-OMON53059

Source
ToetsingOnline

Brief title
MeninGene

Condition

- Bacterial infectious disorders
- Central nervous system infections and inflammations

Synonym
bacterial meningitis; bacterial infection of the membranes lining the brain

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: Cohort, Genetics, Meningitis, Treatment

Outcome measures

Primary outcome

Online case-record forms will be used to collect data on patients* history, symptoms and signs on admission, laboratory findings at admission, treatment (including adjunctive treatment), clinical course, outcome and neurological findings at discharge. Severity and clinical deterioration will be evaluated. Data on complications will be collected according to predefined criteria. Results of neuroimaging will be collected. At discharge, all patients undergo a neurological examination performed by a neurologist, and the outcome is graded according to the Glasgow outcome scale. A score of 1 on this scale indicates death; a score of 2, a vegetative state (the patient is unable to interact with the environment); a score of 3, severe disability (the patient is unable to live independently but can follow commands); a score of 4, moderate disability (the patient is capable of living independently but unable to return to work or school); and a score of 5, mild or no disability (the patient is able to return to work or school). A favourable outcome will be defined as a score of 5, and an unfavourable outcome as a score of 1 through 4. The Glasgow outcome scale is a well-validated instrument with good inter-observer agreement.

Secondary outcome

Niet van toepassing

Study description

Background summary

Meningitis is an inflammation of the membranes covering the brain and spinal cord (the meninges). Each year 35,000 European patients suffer from bacterial meningitis, leaving 7000 deaths and 7000 disabled.1,2 In developing countries, the burden of disease is up to 20 times higher.3,4 Streptococcus pneumoniae and Neisseria meningitidis are the most common etiologic agents accounting for 85% of total cases.1 Although these bacteria are common inhabitants of the human upper respiratory tract, in some individuals they spread to the bloodstream, slip through the blood-brain barrier and cause meningitis, with devastating consequences. Differences in susceptibility and outcome between individuals and populations are poorly understood but genetics of host and pathogen are considered crucial in this host-pathogen interaction.5,6 Recent studies have shown that both host and pathogen genetic characteristics influence the risk of acquiring meningitis, the response to treatment in bacterial meningitis patients and the risk of unfavourable outcome.7-11,13 However, all of these studies used a candidate single-nucleotide polymorphism approach, which is unable to detect novel genetic variants influencing the disease and is likely to overlook the most important genetic risk factors. In the recent years high throughput sequencing methods have enabled massive parallel sequencing of genes and whole genomes.

By sequencing whole genes in patients and whole genomes of bacteria we will be able to
- Determine genetic risk factors for susceptibility to meningitis
- Determine genetic risk factors for unfavourable outcome, cerebrovascular complications and death
- Determine virulence factors in the bacterial genomes

This may improve patient*s care in the following ways:
- By determining genetic risks factor for increased susceptibility to bacterial meningitis protective measures such as vaccination and patient education on early symptoms can be implemented. This will especially be useful patients with recurrent meningitis and families with high incidence of meningitis, in which genetic counselling may be given.
- By determining genetic risk factors for complications or unfavourable outcome new treatments can be devised which counteract the pathophysiological mechanism that leads to the increased disease severity.
- Genotypes may be used to identify patients at high risk for specific complications. Physicians may, in the future, be able to use genetic information to tailor immune-based therapy to modulate the response in a given patient. Future therapeutic trials are likely to be designed to target specific genotypes and associated cellular responses, thereby maximizing clinical

response and patient safety.14
- Identification of genetic variants in bacteria causing increased virulence could lead to development of new vaccines that includes antigens specific for virulent bacteria. This may result in vaccines preventing severe cases of bacterial meningitis.

Study objective

The main objective of the MeninGene study is to identify genetic risk factors in host and pathogen influencing susceptibility to bacterial meningitis, and the rate of complications, unfavourable outcome and death.

Study design

We will conduct a prospective observational nation-wide cohort study in which we will perform massive parallel sequencing of causative bacteria and genes in patients and controls involved in the immune response in bacterial meningitis.

Study burden and risks

Patients do not have direct benefit from this study. Therapies identified as a result of this study may be beneficial to a future episode of meningitis in patients with recurrent meningitis (approximately 5%). The risks of the study are limited to those of a venous blood withdrawal, which are minor.

Contacts

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adolescents (16-17 years)
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age >= 16 yr
2. Bacterial meningitis defined by positive bacterial culture or PCR of cerebrospinal fluid

Exclusion criteria

1. Neurosurgical operation in the month previous to the meningitis episode
2. Head trauma in the month previous to the meningitis episode
3. Presence of neurosurgical devices in the central nervous system such as cerebrospinal fluid catheters or deep brain neurostimulator.

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):	29-04-2013
Enrollment:	3000
Type:	Actual

Ethics review

Approved WMO Date:	18-03-2013
Application type:	First submission
Review commission:	METC Amsterdam UMC
Approved WMO Date:	26-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	29-08-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	14-10-2013
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	28-03-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	08-04-2014
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO	

Date: 18-08-2014

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 19-08-2014

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 21-10-2014

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 31-10-2014

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 10-12-2014

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 16-12-2014

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 16-01-2015

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 10-03-2015

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO
Date: 19-05-2015

Application type: Amendment

Review commission: METC Amsterdam UMC

Approved WMO

Date:	26-06-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	13-10-2015
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-09-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	25-11-2016
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	19-11-2018
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	18-01-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	04-02-2021
Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	24-02-2021
Application type:	Amendment
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Approved WMO	

Date:	23-03-2021
Application type:	Amendment
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Approved WMO Date:	21-04-2021
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Approved WMO Date:	07-07-2021
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Review commission:	METC Amsterdam UMC
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Application type:	Amendment
Review commission:	METC Amsterdam UMC
Approved WMO Date:	30-03-2022
Application type:	Amendment
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	NL43784.018.13