Genetics and outcome of bacterial meningitis

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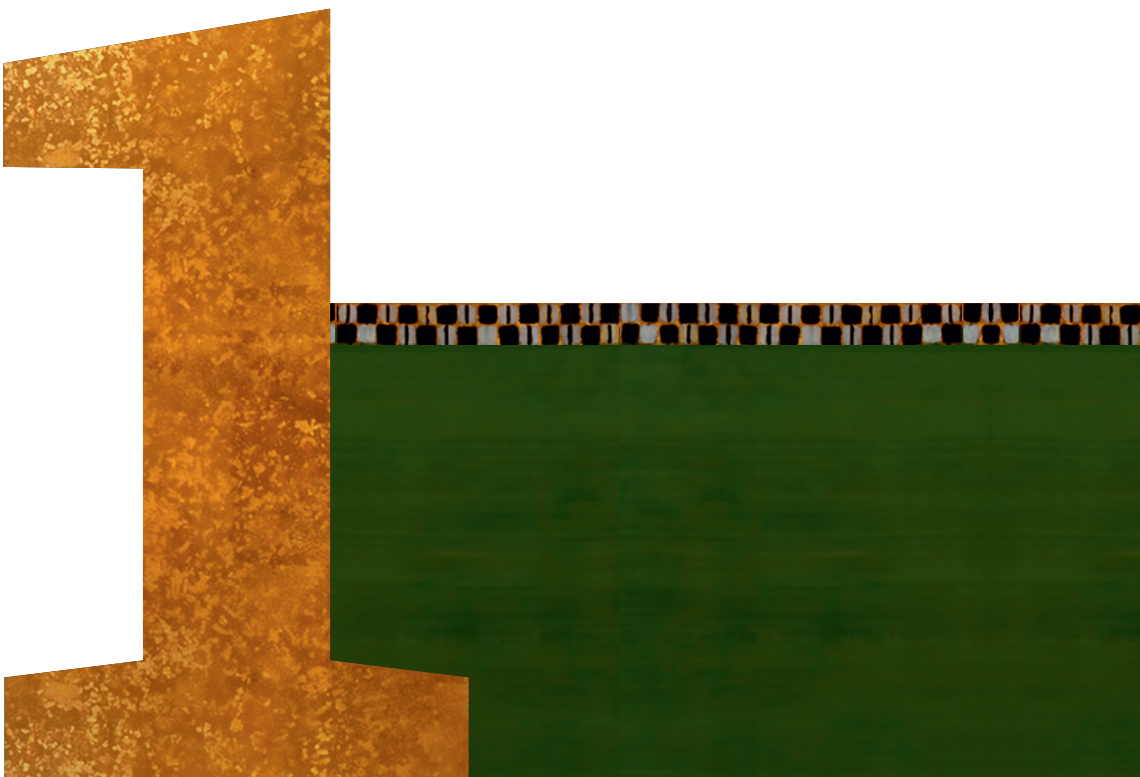
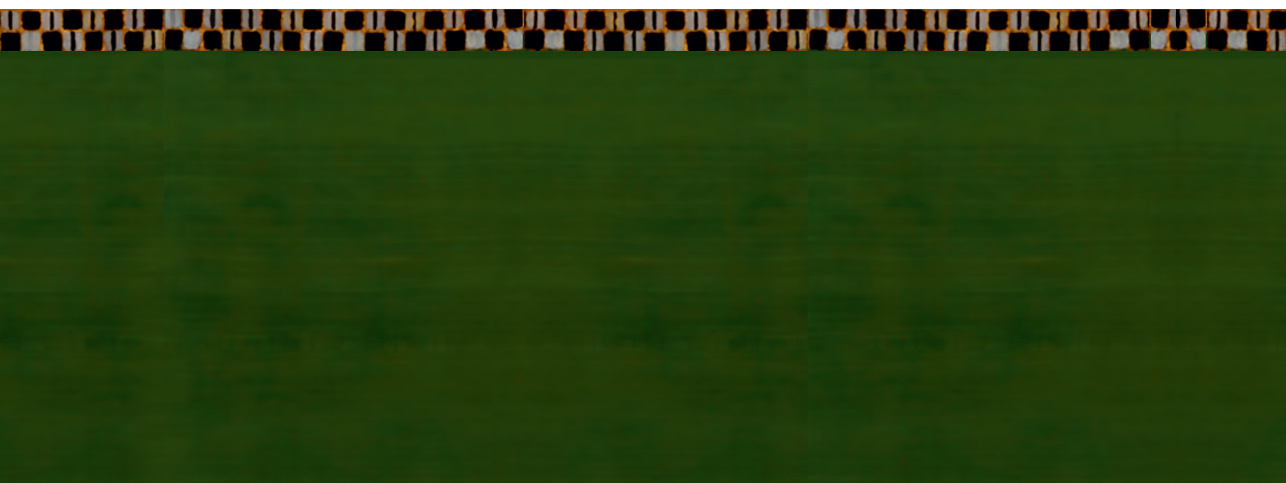
CHAPTER



Introduction



Bacterial meningitis is a devastating disease in which bacteria invade the central nervous system infecting the subarachnoid space and meninges. Affected persons suffer from a substantial morbidity and mortality reflected by an estimated 379,200 deaths in 2015 and 11 million disability adjusted life years in 2017 attributed to bacterial meningitis worldwide.[1,2] The incidence of adult community-acquired bacterial meningitis has been rapidly declining over the last decades since introduction of *Haemophilus influenzae, Neisseria meningitidis and Streptococcus pneumoniae* vaccines in national childhood immunization programmes.[3-5] In poor resource countries, especially in sub-Saharan Africa, incidence rates vary between 10 and 40 per 100,000 inhabitants, whereas in the United States and Europe, incidence rates declined to 0.7 per 100,000.[6-8] Nowadays, outside the neonatal age the most common pathogen in high income countries is the *Streptococcus pneumoniae* (~60%) and on the second place *Neisseria meningitidis* (~10%).[9]

Bacteria are transmitted from person to person through droplets of respiratory or throat secretions. After transmission bacteria can be present as commensals in the nasopharynx and are mostly cleared by the host or competitive pathogens, rather than causing invasive disease.[10] In adults pneumococcal carrier rates of 26% and meningococcal carrier rates of 10-35% are described and it is likely that, at one time or another, during life most individuals are colonized with these pathogens.[10,11] How colonization in the host progresses to disease is not fully understood and this is possibly due to an interaction between environmental, bacterial virulence and host susceptibility factors.

Risk factors increasing host susceptibility to bacterial meningitis are an immunocompromised state due to alcoholism, human immunodeficiency virus (HIV) infection, diabetes mellitus, the use of immunosuppressive drugs, asplenia, and cancer.[4] In the past decades extreme phenotype studies in patients with recurrent or familial disease have identified genetic defects in the immune system to increase susceptibility to meningococcal and pneumococcal meningitis.[12] Subsequently case–control and cohort studies described genetic variation to increase susceptibility to bacterial meningitis.[12]

Adults with bacterial meningitis usually present with headache, nausea, vomiting and photophobia and about half of the patients present with the triad of fever, altered mental status and neck stiffness.[13] Early recognition of the disease is important to accelerate adequate treatment. If bacterial meningitis is suspected clinically, a lumbar puncture should be performed to enable examination of the cerebrospinal fluid (CSF). Definitive diagnosis of bacterial meningitis is made if the CSF shows typical abnormalities in combination with a positive CSF culture.[14]

Despite timely diagnosis and adequate treatment with antibiotics and dexamethasone the mortality of bacterial meningitis is still high, and can be up to 51% depending on the causative pathogen and country income status.[4,13] Up to half of the survivors of bacterial meningitis suffer from neurological and neuropsychological sequelae, like hearing loss (22-69%), epilepsy (4-31%), focal neurological deficits (11-36%) or cognitive impairments (32%).[15,16] Even patients with a good recovery of bacterial meningitis experience a lower quality of life, especially in the subgroup of pneumococcal meningitis patients.[17]

Several host factors are identified that predict unfavourable outcome of bacterial meningitis, such as a low coma score on admission, a low CSF white blood cell count, and elevated serum inflammation markers.[18] These predictors explain part of the inter-individual differences in outcome but leave a substantial part unclarified. Besides immune deficiencies leading to uncontrolled infection, the immune response itself can controversially lead to brain damage and adverse disease outcome.[19] Experimental models of bacterial meningitis have shown anti-inflammatory treatment can reduce the severity of brain and CSF inflammation and lower the risk for adverse outcome and neurological sequelae.[19]

However, in humans, many questions remain unanswered about the host inflammatory response in respect to disease susceptibility and outcome. In the past twenty years, host genetic variation is studied in several cohort studies for their contribution to outcome of disease and these have identified risk genes contributing to unfavourable outcome.[20-22]. The last years, high-throughput genotyping methods resulted in a shift away from the candidate SNP approach to genome-wide association studies (GWAS).[23] These new methods have found even more disease loci, but understanding of how these variants predispose individuals to disease or unfavourable outcome remains limited. Functional understanding of these variants is needed for better insight in pathogenesis of disease and drug discovery.[24]

Aim and outline of this thesis:

The first aim of this thesis is to study the epidemiology, clinical characteristics, outcome and long-term neurological sequelae of bacterial meningitis after the introduction of adjunctive dexamethasone therapy and nationwide implementation of childhood vaccines. Besides useful information for clinicians this will help researches to point out suitable outcome measures for future therapeutic studies. This is addressed in **chapter 2, 3, and 4** by evaluating clinical data of a nationwide prospective cohort study and a follow up study including adults with community-acquired bacterial meningitis. The second aim of this thesis is to gain more insight in bacterial meningitis pathogenesis to develop new preventive strategies and to find targets for adjuvant treatment. In **chapter 5** this aim is addressed by a protein

expression analysis to gain more insight in the expression of inflammatory proteins in the acute phase of disease and related to outcome of disease. Finally, **chapter 6, 7, and 8** describe genetic association studies focussing both on susceptibility and outcome of bacterial meningitis and invasive pneumococcal disease.

In **chapter 2** a nationwide prospective cohort study is presented describing the epidemiology, clinical characteristics and outcome of 1,412 adults with community-acquired bacterial meningitis. These patients were identified between January 2006 and July 2013 by the National Reference Laboratory for Bacterial Meningitis or individual physicians after which clinicians prospectively evaluated included patients by filling in an online database.

Chapter 3 presents the results of a cross sectional cohort study on long-term neurologic, cognitive, and quality of life outcome in adults surviving pneumococcal meningitis. In this study 80 adult survivors of community-acquired pneumococcal meningitis from a Dutch nationwide prospective cohort study underwent neuropsychological tests 1 to 5 years after acute illness. The control group consisted of 69 partners or proxies of patients.

The results of a study assessing the prevalence of sleep impairment in adult survivors of pneumococcal meningitis and its effect on quality of life are presented in **chapter 4**. In this study the same patients and controls as discussed in chapter three were asked to fill in questionnaires about their mental state, quality of sleep and quality of life.

In **chapter 5** two studies are introduced studying the pathogenesis of pneumococcal meningitis by cytokine expression analyses. The role of macrophage migration inhibitory factor (MIF) is studied, which is an inflammatory cytokine and has been shown in an earlier genetic association study to be related with the morbidity and mortality of pneumococcal meningitis. The first study describes MIF measurements in blood samples of 54 bacterial meningitis patients during the acute phase of disease. In a follow up study 80 patients with pneumococcal meningitis were recalled for whole blood and peripheral blood mononuclear cell (PBMC) stimulation to study MIF expression and the relation with cognitive impairment.

In **chapter 6** the results are shown of a genetic association study in 469 community-acquired pneumococcal meningitis cases and 2072 population-based controls from the Utrecht Health Project in order to find genetic variants associated with pneumococcal meningitis susceptibility. In this study a human Exome BeadChip was used to genotype 102,097 single nucleotide polymorphisms (SNPs) in the collected DNA material of the patients and controls.

The next study presented in **chapter 7** aims to investigate whether genetic variation in coagulation and fibrinolysis genes contributes to cerebrovascular complications in bacterial meningitis. In this genetic association study the exons and flanking regions of 16 candidate genes involved in coagulation and fibrinolysis pathways of 622 adult with community-acquired bacterial meningitis patients were sequenced. Next it was analysed if genetic variation in these genes resulted in a higher risk of cerebrovascular complications, unfavorable outcome and differences in thrombocyte count on admission.

Chapter 8 shows the results of a systemic overview of genetic variants associated with susceptibility, phenotype and outcome of community acquired pneumococcal pneumonia (CAP) and invasive pneumococcal disease (IPD). The PubMed search focussed on studies between Jan 1, 1983 and Jul 4, 2018 yielded 1219 studies of which 60 studies involving 15,358 patients were included in the review and meta-analysis.

The results of the presented studies are summarized in **chapter 9**. Furthermore, in this chapter the implications of the studies are discussed and suggestions for future research are proposed.

References

1. Mortality GBD, Causes of Death C. Global, regional, and national life expectancy, all-cause mortality, and cause-specific mortality for 249 causes of death, 1980-2015: a systematic analysis for the Global Burden of Disease Study 2015. Lancet 2016;388:1459-544.
2. DALYs GBD, Collaborators H. Global, regional, and national disability-adjusted life-years (DALYs) for 359 diseases and injuries and healthy life expectancy (HALE) for 195 countries and territories, 1990-2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet 2018;392:1859-922.
3. Bijlsma MW, Bekker V, Brouwer MC, Spanjaard L, van de Beek D, van der Ende A. Epidemiology of invasive meningococcal disease in the Netherlands, 1960-2012: an analysis of national surveillance data. The Lancet Infectious diseases 2014;14:805-12.
4. Brouwer MC, Tunkel AR, van de Beek D. Epidemiology, diagnosis, and antimicrobial treatment of acute bacterial meningitis. ClinMicrobiolRev 2010;23:467-92.
5. McIntyre PB, O'Brien KL, Greenwood B, van de Beek D. Effect of vaccines on bacterial meningitis worldwide. Lancet 2012;380:1703-11.
6. Castelblanco RL, Lee M, Hasbun R. Epidemiology of bacterial meningitis in the USA from 1997 to 2010: a population-based observational study. The Lancet Infectious diseases 2014;14:813-9.
7. Polkowska A, Toropainen M, Ollgren J, Lyytikainen O, Nuorti JP. Bacterial meningitis in Finland, 1995-2014: a population-based observational study. BMJ Open 2017;7:e015080.
8. Kambire D, Soeters HM, Ouedraogo-Traore R, et al. Nationwide Trends in Bacterial Meningitis before the Introduction of 13-Valent Pneumococcal Conjugate Vaccine-Burkina Faso, 2011-2013. PloS one 2016;11:e0166384.
9. van de Beek D, Cabellos C, Dzupova O, et al. ESCMID guideline: diagnosis and treatment of acute bacterial meningitis. Clinical microbiology and infection : the official publication of the European Society of Clinical Microbiology and Infectious Diseases 2016;22 Suppl 3:S37-62.
10. Caugant DA, Maiden MC. Meningococcal carriage and disease--population biology and evolution. Vaccine 2009;27 Suppl 2:B64-70.
11. Adegbola RA, DeAntonio R, Hill PC, et al. Carriage of Streptococcus pneumoniae and other respiratory bacterial pathogens in low and lower-middle income countries: a systematic review and meta-analysis. PloS one 2014;9:e103293.
12. Brouwer MC, de Gans J, Heckenberg SG, Zwinderman AH, van der Poll T, van de Beek D. Host genetic susceptibility to pneumococcal and meningococcal disease: a systematic review and meta-analysis. Lancet InfectDis 2009;9:31-44.
13. van de Beek D, de Gans J, Spanjaard L, Weisfelt M, Reitsma JB, Vermeulen M. Clinical features and prognostic factors in adults with bacterial meningitis. NEnglJMed 2004;351:1849-59.
14. Brouwer MC, Thwaites GE, Tunkel AR, van de Beek D. Dilemmas in the diagnosis of acute community-acquired bacterial meningitis. Lancet 2012;380:1684-92.

15. Lucas MJ, Brouwer MC, van de Beek D. Neurological sequelae of bacterial meningitis. The Journal of infection 2016;73:18-27.
16. Hoogman M, van de Beek D, Weisfelt M, de Gans J, Schmand B. Cognitive outcome in adults after bacterial meningitis. JNeurolNeurosurgPsychiatry 2007;78:1092-6.
17. van de Beek D, Schmand B, de Gans J, et al. Cognitive impairment in adults with good recovery after bacterial meningitis. JInfectDis 2002;186:1047-52.
18. Weisfelt M, van de Beek D, Spanjaard L, Reitsma JB, de Gans J. Clinical features, complications, and outcome in adults with pneumococcal meningitis: a prospective case series. Lancet Neurol 2006;5:123-9.
19. Mook-Kanamori BB, Geldhoff M, van der Poll T, van de Beek D. Pathogenesis and pathophysiology of pneumococcal meningitis. ClinMicrobiolRev 2011;24:557-91.
20. Brouwer MC, Read RC, van de Beek D. Host genetics and outcome in meningococcal disease: a systematic review and meta-analysis. Lancet InfectDis 2010;10:262-74.
21. Geldhoff M, Mook-Kanamori BB, Brouwer MC, et al. Genetic variation in inflammasome genes is associated with outcome in bacterial meningitis. Immunogenetics 2013;65:9-16.
22. Mook-Kanamori BB, Valls Seron M, Geldhoff M, et al. Thrombin-activatable fibrinolysis inhibitor influences disease severity in humans and mice with pneumococcal meningitis. Journal of thrombosis and haemostasis : JTH 2015;13:2076-86.
23. Wijmenga C, Zhernakova A. The importance of cohort studies in the post-GWAS era. Nat Genet 2018;50:322-8.
24. Albert PR. What is a functional genetic polymorphism? Defining classes of functionality. J Psychiatry Neurosci 2011;36:363-5.