Bacterial meningitis in adults: clinical characteristics, risk factors and adjunctive treatment

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Chapter 12

Discussion

Introduction

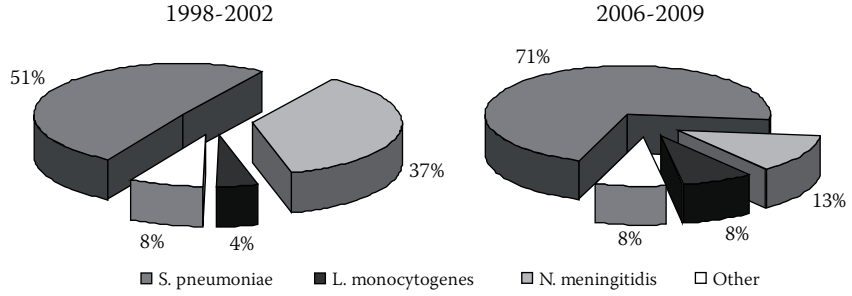
The first objective of this thesis was to describe the epidemiology, diagnostics and treatment of acute bacterial meningitis. This was done with a review of the literature and three studies on less common causes of bacterial meningitis derived from a prospective cohort study performed from 1998-2002. The second objective was to evaluate the role of adjunctive dexamethasone in the treatment of bacterial meningitis. We updated the Cochrane meta-analysis of randomized controlled trials and performed a nation-wide study on the implementation of dexamethasone in pneumococcal meningitis. During this evaluation we observed a new and severe complication in pneumococcal meningitis possibly related to dexamethasone use, described as delayed cerebral thrombosis. The final objective of this thesis was to evaluate genetic risk factors for susceptibility and outcome in bacterial meningitis. We performed two systematic reviews and meta-analyses on studies evaluating genetic risk factors for susceptibility in pneumococcal en meningococcal disease, and outcome in meningococcal disease. In a nation-wide prospective genetic association study we evaluated the association of genetic polymorphisms in the complement system with susceptibility and outcome of bacterial meningitis.

In this chapter, we will place the main findings of this thesis in a broader perspective. We will discuss methodological issues related to our study designs and provide recommendations for future research.

Clinical characteristics

The epidemiology of bacterial meningitis in the developed world has changed in the past 20 years. The basis of this change has been the introduction of conjugated vaccines against *Haemophilus influenzae* and *Streptococcus pneumoniae*.[1,2] Due to the resulting decrease in pediatric bacterial meningitis caused by these pathogens, bacterial meningitis became a disease of adults, predominantly caused by *S. pneumoniae*.[3,4,chapter 7] A further change in epidemiology observed in our studies was the decrease in *Neisseria meningitidis* meningitis from 37 to 14% of adult bacterial meningitis cases in adults in the Netherlands (Figure 1).[5, chapter 7] This caused a further increase in median age of bacterial meningitis patients from 52 to 60 years (Table 1).

Figure 1. Causative organisms of adult bacterial meningitis in the Netherlands.[a]



[a] Data from 696 episodes included from 1998-2002 and 518 from 2006-2009.3, chapter 7

Table 1. Epidemiology and median age of bacterial meningitis in Dutch adults.

Causative organism	1998-2002	Median age (IQR)	2006-2009	Median age (IQR)
All patients	696	52 (32-67)	518	60 (43-70)
S. pneumoniae	352 (51%)	60 (46-71)	357 (69%)	61 (50-71)
N. meningitidis	257 (38%)	30 (19-50)	73 (14%)	34 (19-49)
L. monocytogenes	30 (5%)	65 (55-72)	25 (5%)	63 (49-75)
Other	57 (8%)	59 (44-71)	63 (12%)	63 (41-73)

As a result of the increasing age of the bacterial meningitis population *Listeria monocytogenes* needs to be considered more often as this disease is primarily seen in patients over 50 years old.[6] In our cohort study of 30 *L. monocytogenes* meningitis cases we found that patients present with signs and symptoms that are similar to those of the general population with bacterial meningitis, albeit with a longer prodromal phase. Typical cerebrospinal fluid findings predictive for bacterial meningitis might be absent in *L. monocytogenes* meningitis. Treatment guidelines indicate that patients at risk for *L. monocytogenes* meningitis should receive empirical antimicrobial treatment including amoxicillin since 3rd generation cephalosporins are inactive against this pathogen.[4,7] In our cohort we observed that 30% of patients received inadequate antimicrobial therapy.[6] Increased awareness of *L. monocytogenes* meningitis and adherence to treatment guidelines is essential to prevent a delay in adequate therapy.[8]

Following the success of *H. influenzae* type b conjugate vaccines, *H. influenzae* meningitis in the US and Europe has become a disease predominantly found in adults. In our prospective evaluation of adult patients with community-acquired bacterial meningitis in the Netherlands, we found that *H. influenzae* is a relatively benign disease compared to pneumococcal meningitis, and is often associated with otitis, sinusitis and remote neurosurgery or head trauma.[9] Hearing loss is a frequent complication, occurring in 25% of patients.

Another change in epidemiology has been the increasing resistance to common antibiotics. This has become a major problem in treatment of bacterial meningitis in the last decades, although there is a wide variation in resistance rates per geographical region.[3,4,7,10] *S. pneumoniae* strains have become increasingly resistant to penicillin and third generation cephalosporins, and multidrug-resistant bacteria have been reported to result in treatment failures in patients with pneumococcal meningitis. Vaccination with PCV7 was aimed to decrease the number of highly resistant strains, but has only temporarily decreased the total resistance rate.[11] In the Netherlands pneumococcal resistance rates found in two nationwide cohort studies was very low: only two pneumococcal strains (0.5%) in each cohort showed intermediate resistance to penicillin.[12,chapter 7] Therefore penicillin monotherapy is still the recommended treatment for adult patients up to 50 years old without immunodeficiency (including cancer, diabetes and alcoholism) as almost all episodes in these patients are caused by *S. pneumoniae* and *N. meningitidis*.[3] The adherence to treatment guidelines in the Netherlands is however, persistently low. In two nation-wide studies only 33% of patients received antibiotic treatment in compliance with the guidelines.[8,chapter 7] Continuous surveillance will remain crucial to detect emerging resistance and changes in epidemiology.

Adjunctive dexamethasone treatment

In a systematic review and meta-analysis we found that adjunctive dexamethasone reduced overall hearing loss, severe hearing loss and short term neurologic sequelae in bacterial meningitis.[chapter 6] The reduction in hearing loss was found in both children and adults, while less neurologic sequelae were found in children. In pneumococcal meningitis patients we observed a decline in mortality with a risk ratio of 0.84 (95% confidence interval 0.72 to 0.98) indicating a number needed to treat of 6 patients with pneumococcal meningitis to prevent one death. The beneficial effect of adjunctive dexamethasone was limited to high income countries. Possible explanations for the difference between high and low income countries could be a delayed presentation, differences in clinical severity, underlying anemia, malnutrition, the antibiotics used, HIV infection or other, unidentified differences between populations.

The results of our meta-analysis should be interpreted with caution as the high quality studies in the meta-analysis showed no effect of corticosteroid treatment. The beneficial effect was mostly found in studies of median and low quality which did not address missing data or failed to perform an intention to treat analysis. Other biases in these studies were patient selection, withdrawal of patients, competitive risks between outcome measures and heterogeneity between studies with respect to study protocol. A meta-analysis of individual patient data of five recent large trials did not identify a beneficial effect from dexamethasone in any pre-specified subgroups.[13] A post-hoc analysis in the same study showed a lower rate of hearing loss in survivors treated with dexamethasone. Due to the biases in our meta-analysis and the lack of effect on pre-specified outcome measures in the individual patient data meta-analysis, there is still uncertainty about the effectiveness of adjunctive dexamethasone. A new trial on adjunctive dexamethasone would need to include approximately 13.500 patients to show an odds ratio of 0.9 with a power of 90% in a population with 27% risk of death in the placebo group, and is therefore unlikely to be performed or finished in the next decade. Follow-up studies in countries where dexamethasone has been implemented could provide circumstantial evidence about its effectiveness.

In our evaluation of the implementation and effectiveness of adjunctive dexamethasone in the Netherlands, we found that in 92% of episodes adjunctive dexamethasone was given and in 84% of episodes dexamethasone was started before or with the antibiotics. A 10% decrease in case fatality rate and unfavorable outcome rate was found when comparing cohort studies performed before and after implementation of dexamethasone. Using a multivariate prognostic model we calculated the expected number of events if dexamethasone would not have been introduced and compared these with the actually observed number of patients with unfavorable outcome. The observed unfavorable outcome rate was 10% lower than calculated with the prognostic model. A 13% difference between expected and observed unfavorable outcome rate was found in patients receiving the standard dexamethasone regimen. The observed unfavorable outcome rate in the patients that did not receive dexamethasone was exactly as predicted by the prognostic model. This study shows that adjunctive dexamethasone has been successfully implemented in the Netherlands and that

the prognosis on a national level has improved significantly with a decrease in mortality from 30 to 20%.

Results of studies using historical controls have to be interpreted with caution as they can be distorted by unknown differences between treatment groups. These differences can only be eliminated by randomization. In our study we corrected for all known prognostic factors in pneumococcal meningitis and compared two nation-wide cohorts of pneumococcal meningitis patients included on an intention to treat basis. The observed decrease in case fatality rate was similar to that observed in a randomized controlled trial on adjunctive dexamethasone in bacterial meningitis, performed mainly in Dutch patients. The only identified difference in treatment between groups was adjunctive dexamethasone and the improved outcome was exclusively seen in dexamethasone-treated patients. Although a true effect of dexamethasone seems likely, the possibility of unknown outcome modifiers can not be excluded.

The optimal timing of corticosteroids treatment was examined in a subgroup analysis in the Cochrane meta-analysis, but no differences in effect were identified between patients receiving steroids before or with the first dose of antibiotics compared to those receiving steroids after the antibiotics. In our prospective cohort study on the implementation of adjunctive dexamethasone we found that the difference between unfavorable outcome predicted by the multivariate prediction model and the observed unfavorable outcome was larger in patients who did not receive pre-treatment with antibiotics.[chapter 7] This suggests that dexamethasone is more effective when given with or before the antibiotics.

We identified a new complication in pneumococcal meningitis which was possibly related to adjunctive dexamethasone treatment.[chapter 8] Six patients with an initial excellent recovery from pneumococcal meningitis developed a similar clinical picture with sudden deterioration after 7-19 days with headache, fever, a decreased level of consciousness, brainstem signs, or hemiparesis. Imaging studies showed infarctions involving the thalamus or brainstem in all patients. Pathological examination showed massive thrombosis in the penetrating arteries of the posterior circulation without vasculitis, suggesting an immunologic reaction targeting cerebral blood vessels. This complication was not reported before and has not been identified in the 1998-2002 cohort study when only 3% of patients received dexamethasone. A possible explanation for this syndrome could be the upregulation of tumor growth factor β receptor 2 by dexamethasone, which is related to cerebral vasculitis in pneumococcal meningitis. An additional explanation could be a rebound effect of the primary inflammatory reaction initially suppressed by dexamethasone. Only two out of six patients survived and both of them received a prolonged course of high dose steroids upon deterioration.

We conclude that the available evidence indicates that adjunctive dexamethasone is effective in preventing hearing loss in both adults and children with bacterial meningitis in high income countries, and is associated with a 10% absolute reduction in case fatality rate in pneumococcal meningitis. In high income countries a four day course of adjunctive dexamethasone should be given with or before the first dose of antibiotics. When pneumococcal meningitis is complicated by delayed cerebral thrombosis we advise reinitiation of high dose dexamethasone followed by gradual tapering.

Genetics in bacterial meningitis

In the 1980s, adoption and twin studies showed that genetics are major determinants of susceptibility to infectious diseases.[14,15] Defects in innate immunity were described to be associated with pneumococcal and meningococcal infections within families.[16-18] New technologies provided the opportunity to study the genetic basis of susceptibility to these diseases. Our review and meta-analysis of studies on susceptibility to pneumococcal and meningococcal infections showed that genetic polymorphisms in the complement system and pattern recognition pathways were found in patients with recurrent or familial episodes of pneumococcal and meningococcal diseases. These polymorphisms are rare in the normal population, but are associated with a substantial increase in susceptibility.

Single base-pair alterations (single nucleotide polymorphisms [SNPs]) occur regularly in genes controlling the host response to microbes and are thought to influence susceptibility to infections.[19] Case-control studies were performed to identify common SNPs that increased susceptibility to pneumococcal and meningococcal disease. We found that most of these studies had methodological flaws, mostly a small sample size. Despite these flaws genetic variants in the complement system, pattern recognition receptor pathways, cytokines and nasopharyngeal adhesion molecules were risk factors for developing pneumococcal or meningococcal disease.

The severity and outcome of meningococcal disease is highly variable between patients. The clinical spectrum includes fulminant meningococcal sepsis, meningococcal meningitis and chronic meningococcemia. The basic cause of differences between individuals within this clinical spectrum of meningococcal disease is unclear. Genetic variation is thought to influence coagulation, fibrinolysis, and cytokine activation in meningococcal disease and thereby affect outcome, disease severity or disease phenotype. In our review of studies on genetic polymorphisms in relation to outcome we found that SNPs in immunoglobulin receptors, fibrinolysis (plasminogen activator inhibitor 1 – *SERPINE1*) and cytokines were risk factors for an unfavorable outcome. SNPs in immunoglobulin receptors and *SERPINE1* were associated with sepsis and diffuse intravascular coagulation.

We evaluated the influence of genetic polymorphisms on susceptibility, complications and outcome in community-acquired bacterial meningitis patients in a nation-wide prospective genetic association study. We selected common, uncommon and previously studied SNPs in pathways of pathophysiological interest in bacterial meningitis. This included the complement system, pattern recognition receptor pathways, fibrinolysis and coagulation pathway, and cytokines. We found that a common polymorphism in complement factor 3 was associated with susceptibility and a common polymorphism in complement factor 5 with unfavorable outcome. Uncommon SNPs related to susceptibility were identified in complement factor 5 and D. An uncommon SNP in complement factor 8 was associated with unfavorable outcome. Complement factor 3 and 5 have a central role in all three complement activation pathways. The importance of complement factor 3 in susceptibility to pneumococcal infections has been shown in animal models.[20-22] In experimental meningitis models inhibition of complement factor 5 resulted in less CSF white cell influx into CSF. A low CSF white cell count is a strong risk factor for unfavorable outcome in

bacterial meningitis.[3] In our genetic association study we found that patients with a complement factor 5 variant have less CSF white cell counts and a higher rate of unfavorable outcome. These results suggest a central role of the complement system in susceptibility and outcome of bacterial meningitis.

We replicated the previously found association of complement factor mannose binding lectin SNPs and the pro-inflammatory cytokine tumor necrosis factor alpha with bacterial meningitis.[Chapter 11] We also confirmed the association of nuclear factor kappa B inhibitor A (*NFKBIA*) with susceptibility to pneumococcal meningitis. NFKBIA inhibits a common intracellular signaling cascade that occurs after innate immune system activation by pattern recognition receptors and cytokines that results in transcription of pro-inflammatory genes. We found that common complications of bacterial meningitis are influenced by genetic polymorphisms. The *SERPINE1* polymorphism was associated with cerebral infarctions which resulted in a higher rate of unfavorable outcome. This *SERPINE1* SNP influences fibrinolysis activity and presents a possible target for future therapy. A SNP in anti-inflammatory cytokine interleukin-1 receptor antagonist was identified to be a risk factor for septic shock. Identification of patients at risk for sepsis by genotyping can be used to intensify supportive care or transfer patients to high care facilities.

With our studies we show that genetic polymorphisms are important risk factor for developing bacterial meningitis and influence the rate of complications and unfavorable outcome. This provides new insight into the pathogenesis of bacterial meningitis and presents potential targets for preventive strategies and therapeutic interventions.

Future directions

New studies on genetic risk factors for bacterial meningitis will need to focus on the complement system. The functionality of genetic polymorphisms identified in the complement system in our study is unclear. Although all SNPs were non-synonymous, it is unknown if they change complement activation. Animal bacterial meningitis models can be used to determine the functionality of complement factors in bacterial meningitis with knock-out models and the effect of introducing SNPs on complement activation.

To identify whether the SNPs are isolated or part of haplotype, further genotyping has to be performed. Full sequencing studies of complement genes will identify what combination of SNPs is the strongest risk factor for susceptibility, complications and outcome in bacterial meningitis. Genetic risk factors for invasive infectious disease can be future parameters to determine vaccination strategies. Furthermore, a risk profile for patients admitted with bacterial meningitis based on genetic risk factors can be used to augment supportive therapies. Individualized treatment for patients with genetic risk factors for cerebral infarction of septic shock can be used to improve prognosis.

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