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

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Chapter

1

Introduction

When bacteria cross the physical barriers protecting the central nervous system and invade the subarachnoid space located between the meninges, a severe inflammation of these membranes that envelope the brain and spinal cord, known as bacterial meningitis, is the result. Bacterial meningitis was first described by Hippocrates in the 5th century B.C. in his volume *Diseases II* of the *Corpus Hippocraticum*:¹

Ἄλλη νοῦσος· ῥίγιος καὶ ὀδύνη καὶ πυρετοὶ διὰ τῆς κεφαλῆς, μάλιστα δὲ ἐς τὸ οὖς καὶ ἐς τοὺς κροτάφους καὶ ἐς τὸ βρέγμα, καὶ τὰς χώρας τῶν ὀφθαλμῶν ἀλγέει, καὶ αἱ ὀφρῦες δοκεοῦσιν οἱ ἐπικέεσθαι, καὶ τὴν κεφαλὴν βάρος ἔχει, καὶ ἦν τίς μιν κινήσῃ, ἐμέσει, καὶ ἐμέει πούλῦ καὶ ῥηϊδίως, καὶ τοὺς ὀδόντας ναρκᾶ καὶ αἰμωδίη ἔχει, καὶ αἱ φλέβες αἴρονται καὶ σφύζουσιν αἱ ἐν τῇ κεφαλῇ, καὶ οὐκ ἀνέχεται ἡρεμέων, ἀλλ' ἀλύει καὶ ἀλλοφρονέει ὑπὸ τῆς ὀδύνης. Τοῦτω ἦν μὲν κατὰ τὰς ῥίνας ἢ κατὰ τὰ ὦτα ῥαγῇ, ὕδρωψ ῥεῖ ὑπόπυος, καὶ ὑγῆς γίνεται· ἦν δὲ μὴ, ἀποθνήσκει ἐν ἑπτὰ ἡμέρησιν ὡς τὰ πολλά.

“Chills, pain and fever throughout the head, especially in the ear, temples and bregma. The patient feels pain in the sockets of his eyes, his eyebrows seem to press down on him, and heaviness befalls his head.

If anyone moves him, he vomits copiously and easily; his teeth are set on edge, and he is numb. The vessels in his head are raised up and throb, and he cannot bear to be still, but is besides himself and frenzied from pain.

If, in this patient, a watery discharge breaks out through the nostrils or ears, it runs out mixed with pus, and he recovers; if not, he usually dies in seven days.” (Hp. *Morb ii*, 16).

Bacterial meningitis is a medical emergency which proved uniformly fatal until the early 1920's.² Gaspard Vieusseux was the first to give a detailed description of the clinical syndrome of bacterial meningitis during an epidemic of meningococcal meningitis in Geneva in 1805. With the introduction of the lumbar puncture in 1890 by Heinrich Quincke, the diagnosis could be confirmed with cerebrospinal fluid examination. The introduction of equine antiserum in the 1920's was the first available treatment option and reduced mortality in meningitis due to *Neisseria meningitidis* (meningococcus) and *Haemophilus influenzae* to 20-30%. Meningitis due to *Streptococcus pneumoniae* (pneumococcus) however, remained nearly always fatal. The major reduction in mortality came with the advent of antimicrobial treatment with sulphonamides and penicillin, reducing mortality in meningococcal meningitis to 10% and *H. influenzae* meningitis to 5%.^{2,3} Despite the availability of effective antibiotic therapy mortality in pneumococcal meningitis remained high at 30% throughout the 20th century.^{2,4}

In **Part 1** of this thesis we describe clinical characteristics of bacterial meningitis. **Chapter 2** describes the changing epidemiology of bacterial meningitis throughout the world, by reviewing the global changes in etiologic agents followed by specific microorganism data on the impact of development and widespread use of conjugate vaccines. Recommendations for empirical antimicrobial and adjunctive therapy for clinical subgroups are provided, and available laboratory methods in making the diagnosis of bacterial meningitis are reviewed. Furthermore, risk factors, clinical features and microbiological diagnostics for the specific bacteria causing this disease are described. In **Chapter 3** a nation-wide prospective study on community-acquired bacterial meningitis caused by *Listeria monocytogenes*, the third most common cause of bacterial meningitis, is presented. We describe specific risk factors for developing *Listeria* meningitis, clinical characteristics and complications in a cohort of 30 patients. **Chapter 4** describes the clinical characteristics, complications and prognosis of adults with *Haemophilus influenzae* meningitis. *H. influenzae* used to be the most common cause of bacterial meningitis and predominantly occurred in children. Due to vaccination against *H. influenzae* type B this disease is now rare in children but does still regularly occurs in adults. In **Chapter 5**, a prospective case-series of community-acquired meningitis due to *Staphylococcus aureus* is described.

Experimental models have shown that outcome in bacterial meningitis is related to the severity of inflammation in the subarachnoid space. In these animals models treatment with corticosteroids resulted in a reduction of the inflammatory response and improved outcome.^{5,6} In 2002, a European multicenter randomized clinical trial showed a beneficial effect of adjunctive dexamethasone therapy in adults with bacterial meningitis.⁷ In this clinical trial, treatment with dexamethasone was associated with a reduction in the risk of an unfavorable outcome which was most apparent in the pneumococcal subgroup. However, three other large randomized clinical trials on this topic published in 2007 showed conflicting results.⁸⁻¹⁰ An individual patient data meta-analysis of five large recent randomized controlled trials showed no effect of dexamethasone on mortality, neurological sequelae and severe hearing loss in any of the pre-specified subgroups.¹¹ A post-hoc analysis in the same study did show a reduction in any hearing loss in dexamethasone treated patients. It remains unclear if specific populations do benefit from adjunctive dexamethasone.

In **Part 2** of this thesis we evaluate the role of adjunctive dexamethasone in bacterial meningitis. We performed an update of the Cochrane systematic review and meta-analysis of randomized clinical trials on adjunctive dexamethasone in bacterial meningitis, which is presented in **Chapter 6**. After the European trial showed a beneficial effect of adjunctive dexamethasone, treatment guidelines incorporated dexamethasone as standard therapy in the Netherlands. In **Chapter 7** the implementation of adjunctive dexamethasone therapy in pneumococcal meningitis is evaluated in a nation-wide prospective cohort study from 2006-2009. Data from this cohort are compared to a similar cohort from 1998-2002. Using a multivariate prediction models based on the earlier cohort a risk score was calculated for all patients in the new cohort. By comparing the predicted risk of an unfavorable outcome and mortality rate with the true rate, the effect of the implementation of dexamethasone could be estimated. In **Chapter 8** a novel complication of pneumococcal meningitis is described

which is potentially related to the administration of adjunctive dexamethasone. Six patients with pneumococcal meningitis made an excellent recovery, but suddenly deteriorated and developed multiple infarctions primarily located in the posterior circulation territory, one to two weeks after disease onset. We describe clinical characteristics, radiological examinations and autopsy results of these patients. Data from a literature search for similar cases are presented and we discuss the potential pathophysiology and treatment of this complication.

Several risk factors for bacterial meningitis have been identified, but the basic differences in susceptibility and outcome between individuals and populations are poorly understood.^{4,12} Pneumococcal meningitis has been associated with immunocompromise and with distant foci of infection. Meningococcal meningitis has been associated with smoking and living in the same household as a patient. One additional risk factor for development of meningococcal disease is disease in proxies, which might be explained by increased risk of nasopharyngeal colonization or by genetic preponderance for the disease. In the 1980s, adoption and twin studies showed that genetics are major determinants of susceptibility to infectious diseases.¹² Defects in innate immunity have been described to be associated with susceptibility to pneumococcal and meningococcal infections within families. These studies support the idea that genetics are important in this susceptibility. Single base-pair alterations (single nucleotide polymorphisms [SNPs]) occur regularly in genes controlling the host response to microbes, and may theoretically explain inter individual differences in susceptibility, at least in part.

In **Part 3** of this thesis we focus on the genetic risk factors influencing susceptibility and outcome in bacterial meningitis. In **Chapter 9** the results of a systematic review and meta-analyses on genetic risk factors for developing infections with *S. pneumoniae* and *N. meningitidis* are presented. We scored each study for methodological key issues and evaluated the validity of previously found associations. A systematic review and meta-analysis of studies on genetic polymorphisms influencing outcome in meningococcal disease is presented in **Chapter 10**. Genetic polymorphisms are thought to influence coagulation, fibrinolysis, and cytokine activation in meningococcal disease and thereby affect outcome, disease severity or disease phenotype. In **Chapter 11** results from a genetic association study on the influence of single nucleotide polymorphisms on susceptibility and outcome in bacterial meningitis are presented. Genetic polymorphisms in the complement system, pattern recognition receptor pathways, coagulation factors and cytokines of 439 patients with bacterial meningitis from a nationwide cohort study were compared with 302 age, sex and ethnically matched controls.

This thesis concludes with a general discussion (**Chapter 12**) in which the implications of the presented studies are discussed and suggestions for future research are proposed.

References

1. Edition: É. Littré, Oeuvres complètes d'Hippocrate, vols. 6-7. Paris: Baillière, 1851 (repr. Amsterdam: Hakkert, 1962). Transl.: P. Potter. Hippocrates vol. 5. Cambridge, Massachusetts: Harvard University Press (Loeb); 1988.
2. Swartz MN. Bacterial meningitis--a view of the past 90 years. *N Engl J Med* 2004; 351: 1826-8.
3. Dowling HF, Sweet LK. The treatment of pneumococcal meningitis with massive doses of systemic penicillin. *Am J Med Sci* 1949; 217: 149-56.
4. 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. *N Engl J Med* 2004; 351: 1849-59.
5. Scheld WM, Dacey RG, Winn HR, Welsh JE, Jane JA, Sande MA. Cerebrospinal fluid outflow resistance in rabbits with experimental meningitis. Alterations with penicillin and methylprednisolone. *J Clin Invest* 1980; 66: 243-53.
6. Tauber MG, Khayam-Bashi H, Sande MA. Effects of ampicillin and corticosteroids on brain water content, cerebrospinal fluid pressure, and cerebrospinal fluid lactate levels in experimental pneumococcal meningitis. *J Infect Dis* 1985; 151: 528-34.
7. de Gans J, van de Beek D. Dexamethasone in adults with bacterial meningitis. *N Engl J Med* 2002; 347: 1549-56.
8. Nguyen TH, Tran TH, Thwaites G et al. Dexamethasone in Vietnamese adolescents and adults with bacterial meningitis. *N Engl J Med* 2007; 357: 2431-40.
9. Scarborough M, Gordon SB, Whitty CJ et al. Corticosteroids for bacterial meningitis in adults in sub-Saharan Africa. *N Engl J Med* 2007; 357: 2441-50.
10. Peltola H, Roine I, Fernandez J et al. Adjuvant glycerol and/or dexamethasone to improve the outcomes of childhood bacterial meningitis: a prospective, randomized, double-blind, placebo-controlled trial. *Clin Infect Dis* 2007; 45: 1277-86.
11. van de Beek D, Farrar JJ, de Gans J et al. Adjunctive dexamethasone in bacterial meningitis: a meta-analysis of individual patient data. *Lancet Neurol* 2010; 9: 254-63.
12. Brouwer MC, Read RC, van de Beek D. Host genetics and outcome in meningococcal disease: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; 10: 262-74.