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

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Summary

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Bacterial meningitis is a severe infection of the meninges, the membrane lining of the brain and spinal cord. The most important causative micro-organisms of bacterial meningitis are *Streptococcus pneumoniae* (pneumococcus) and *Neisseria meningitidis* (meningococcus), causing approximately 80% of cases in adults. Despite optimal antibiotic therapy and advances in critical care 1 in 6 patients die from bacterial meningitis and many have neurologic sequelae. Prognosis is especially dismal in pneumococcal meningitis, with 30% of the patients dying and neuropsychological sequelae occurring in half of the survivors with apparent good recovery.

In Chapter 2 of this thesis we describe the epidemiology, clinical characteristics, diagnosis and treatment of bacterial meningitis. Bacterial meningitis used to be a disease predominantly found in infants caused by *Haemophilus influenzae* type B. The incidence of *H. influenzae* type B meningitis in children dramatically decreased after vaccination against this pathogen was initiated in the nineties. The introduction of the 7-valent conjugated pneumococcal vaccine in children in the past decade caused a further decline in pediatric meningitis. Another change in epidemiology was observed in our studies of adult bacterial meningitis. The incidence of meningococcal disease, which occurs mainly in young adults, decreased from 37% to 14% of all meningitis episodes in adults. Due to these changes bacterial meningitis has become a disease primarily found in older adults (mean age 60 years), caused by pneumococci in 70% of cases. Due to a decrease in function of the immune system with age the elderly are at risk for meningitis due to uncommon micro-organisms such as *Listeria monocytogenes*. This bacterium mainly spreads through contaminated food and is especially associated with soft cheese and ready-to-eat deli food. In Chapter 3 of this thesis we describe 30 patients with *Listeria* meningitis who were included between 1998 and 2002 in a nation-wide prospective cohort study. All patients were over 50 years old or were immunodeficient. Meningitis due to *L. monocytogenes* presents with the same symptoms and signs as bacterial meningitis due to other pathogens but needs specific anti-microbial treatment (amoxicillin). In our cohort study we found that 30% of patients with *Listeria* meningitis received inappropriate initial antimicrobial therapy. In Chapter 4 and 5 we discuss other infrequent causes of bacterial meningitis in adults: *Haemophilus influenzae* and *Staphylococcus aureus*. Meningitis due to these bacteria occurs in patients with specific risk factors such as a history of skull fractures, cerebrospinal fluid leakage, otitis or sinusitis (*H. influenzae*) or endocarditis and pneumonia (*S. aureus*).

The second part of this thesis describes the role of adjunctive dexamethasone in bacterial meningitis. Dexamethasone, an anti-inflammatory glucocorticoid, was shown to decrease the severity of the inflammatory response in animal bacterial meningitis models and thereby improved outcome. After this beneficial effect was shown in animal experiments, several trials have evaluated the effect of corticosteroids in bacterial meningitis patients. The initial trials were mostly small and performed in children with *H. influenzae* meningitis, and showed that dexamethasone reduced the rate of severe bilateral hearing loss. In 2002 a large European randomized controlled trial showed that dexamethasone also had a favorable effect on mortality and neurologic sequelae in

adults with bacterial meningitis. This effect was predominantly found in pneumococcal meningitis patients, in whom the case fatality rate was reduced from 30% to 15%. However, in 2007 three other large randomized controlled trials from Malawi, Viet Nam and South America showed no effect of adjunctive dexamethasone. To determine the true effect of dexamethasone we performed a systematic review and meta-analysis in Chapter 6. This study showed that dexamethasone reduced hearing loss in both children and adults. Our meta-analysis also showed that patients with pneumococcal meningitis were less likely to die when given dexamethasone. The beneficial effect of dexamethasone was limited to high income countries. After the European dexamethasone study was published in 2002, Dutch bacterial meningitis treatment guidelines advised adjunctive dexamethasone in all adult patients during the first 4 days of admission. In Chapter 7 we evaluated whether the implementation of adjunctive dexamethasone in the Netherlands changed the prognosis in bacterial meningitis. We prospectively included patients in a nation-wide cohort study with pneumococcal meningitis from March 2009 to January 2010 and compared the patient data with those from a previous cohort study, performed from 1998-2002. The previous cohort study was performed before adjunctive dexamethasone was routinely administered. We found that 92% of pneumococcal meningitis patients received adjunctive dexamethasone between 2006 and 2009. The case fatality rate decreased from 30% in 1996-2002 to 20% in 2006-2009, with similar severity of disease on presentation. Despite the strong improvement in prognosis of pneumococcal meningitis we encountered a new and severe complication, possibly related to dexamethasone use. In Chapter 8 we present 6 patients with an initial excellent recovery from pneumococcal meningitis who suddenly deteriorated after 7-19 days, developing headache, fever, a decreased level of consciousness, brainstem signs, or hemiparesis. Imaging studies showed multiple brain infarctions in the posterior cerebral circulation territory. A possible explanation for this complication could be that dexamethasone upregulates growth factors associated with cerebral vasculitis. An alternative explanation could be that the inflammatory response is initially suppressed by dexamethasone but rebounds after the effect of dexamethasone has worn off. Only two of six patients survived this complication. Both received a high dose of steroids upon deterioration. Therefore reinitiation of dexamethasone is suggested in the treatment of this complication.

The cause of basic differences in susceptibility and outcome in bacterial meningitis between individuals is unknown. Studies in adopted children and twins showed that the risk of developing infectious diseases is strongly hereditary. To determine if and which genetic risk factors predispose to bacterial meningitis we performed two systematic reviews and meta-analysis, presented in Chapter 9 and 10, of genetic association studies performed in patients with pneumococcal or meningococcal infections. We found that small genetic variations (genetic polymorphisms) influence the risk of contracting these diseases. These genetic polymorphisms were principally found in genes coding for proteins involved in recognition of bacteria and the subsequent inflammatory response. For meningococcal disease we found that polymorphisms in the coagulation and fibrinolysis genes strongly influence the risk of dying. To determine the influence of genetic polymorphisms in

susceptibility and outcome of bacterial meningitis we collected DNA from all patients included in a nation-wide prospective cohort study of community acquired bacterial meningitis patients from 2006-2009. We compared genetic polymorphisms of bacterial meningitis patients and compared these with healthy controls (partners). In Chapter 11 we describe the results of this study. We found that common genetic polymorphisms in the complement system, an important part of the innate immune response, strongly influence susceptibility to bacterial meningitis and the risk of an unfavorable outcome. Furthermore we found that genetic variations influenced the risk of developing brain infarctions or septic shock in bacterial meningitis patients.

Recognition of individuals with an increased risk of bacterial meningitis due to their genetic make-up can potentially change prevention strategies (vaccination). Identification of bacterial meningitis patients with a genetically increased risk for complications or an unfavorable outcome could be used to individualize and intensify treatment for the specific complications.