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Neurological sequelae of bacterial meningitis

Marjolein J. Lucas, Matthijs C. Brouwer, Diederik van de Beek*

Department of Neurology, Center of Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, PO Box 22660, 1100DD Amsterdam, The Netherlands

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Summary *Objectives:* We reported on occurrence and impact of neurological sequelae after bacterial meningitis.
Methods: We reviewed occurrence of neurological sequelae in children and adults after pneumococcal and meningococcal meningitis.
Results: Most frequently reported sequelae are focal neurological deficits, hearing loss, cognitive impairment and epilepsy. Adults with pneumococcal meningitis have the highest risk of developing focal neurological deficits, which are most commonly caused by cerebral infarction, but can also be due to cerebritis, subdural empyema, cerebral abscess or intracerebral bleeding. Focal deficits may improve during clinical course and even after discharge, but a proportion of patients will have persisting focal neurological deficits that often interfere in patient's daily life. Hearing loss occurs in a high proportion of patients with pneumococcal meningitis and has been associated with co-existing otitis. Children and adults recovering from bacterial meningitis without apparent neurological deficits are at risk for long-term cognitive deficits. Early identification of neurological sequelae is important for children to prevent additional developmental delay, and for adults to achieve successful return in society after the disease.
Conclusions: Neurological sequelae occur in a substantial amount of patients following bacterial meningitis. Most frequently reported sequelae are focal neurological deficits, hearing loss, cognitive impairment and epilepsy.

* Corresponding author. Department of Neurology, Center of Infection and Immunity Amsterdam (CINIMA), Academic Medical Center, University of Amsterdam, PO Box 22660, 1100DD Amsterdam, The Netherlands. Tel.: +31 205663842; fax: +31 205669374.
E-mail address: d.vandebeek@amc.uva.nl (D. van de Beek).

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Introduction

The estimated incidence of bacterial meningitis is 0.8–2.6 per 100.000 adults per year in developed countries and can be up to 10 times higher in less developed countries.[1–5] Despite the implementation of effective antibiotic therapy, adjunctive dexamethasone therapy and modern intensive care facilities, associated mortality and morbidity rates remain high.[1,3] Predominant causative pathogens beyond the neonatal age are *Streptococcus pneumoniae* and *Neisseria meningitidis*, responsible for 70–80% and 10–20% of bacterial meningitis cases in Europe and the United States.[1,6] Reported case fatality rates vary with age of the patient, causative pathogen and country income status.[6] Meningitis caused by *S. pneumoniae* has the highest case fatality rates, ranging from 20 to 37% in high-income countries and up to 51% for low-income countries.[6] Case fatality rates for meningococcal meningitis are much lower, ranging between 3 and 10% for high- and low-income countries.[7,8] Neurological sequelae have been estimated to occur in a substantial number of surviving patients: about half of survivors suffer from focal neurological deficits, including hearing loss, epilepsy and cognitive impairment.[9–13] Costs associated with post-meningitis sequelae have an important economic impact on health care systems.[14] We reviewed occurrence and impact of neurological sequelae after pneumococcal and meningococcal meningitis.

Methods

For this qualitative review of neurological sequelae after bacterial meningitis we searched PubMed using Entrez for studies on neurological sequelae after pneumococcal and meningococcal meningitis, by use of the terms "*Streptococcus pneumoniae*", "*Neisseria meningitidis*", "meningitis", "sequelae", "cognitive impairment", "hearing loss", "hydrocephalus", "seizures", "epilepsy", "vision loss", "outcome" and "long-term follow-up". Studies were eligible for inclusion if the sequelae were reported per causative pathogen and if sequelae were reported separately for children and adults. We limited the review to bacterial meningitis caused by *S. pneumoniae* and *N. meningitidis*, as these are currently the most common pathogens of bacterial meningitis.[1,6] Sequelae among children and adults were evaluated separately.

Focal neurological deficits

Focal neurological deficits after bacterial meningitis are most commonly caused by cerebrovascular events,[15] but may also be due to other cerebral pathologies, such as subdural empyema,[16] cerebral abscess,[17] or intracerebral bleeding.[18] Invasion of bacteria in the subarachnoid space and brain parenchyma triggers the release of cytokines resulting in severe inflammation.[19] This inflammatory response goes hand in hand with activation of coagulation and inhibition of fibrinolysis in the vasculature, which may result in thrombosis, infarction and haemorrhage.[15,20,21] Focal neurologic deficits due to cerebral infarction may be present on admission (early), develop during clinical course (intermediate), or after initial good recovery (late; *i.e.*, delayed cerebral thrombosis).[15,22] Cerebral infarctions occur in one of four bacterial meningitis patients[15]; focal neurological deficits are present on admission in half of these patients, the other half develop symptoms of infarction during clinical course. Delayed cerebral thrombosis is identified in about 1% of bacterial meningitis patients and mainly occurs in patients with pneumococcal meningitis.[22] Patients with delayed cerebral thrombosis develop headache and focal neurological deficits after initial good recovery, which is most commonly followed by coma, caused by multiple cerebral infarctions. Dexamethasone therapy seems to predispose patients to this complication. Because of the beneficial effect of adjunctive dexamethasone treatment in bacterial meningitis patients, the risk of delayed cerebral thrombosis should not be a ground to withhold dexamethasone.[22]

Children

In a nationwide prospective cohort study including 45 children with pneumococcal meningitis in Denmark, focal neurological deficits (including aphasia, ataxia or paresis) were identified in only one child (3%).[23] An Australian study retrospectively analysed clinical outcome of 57 children aged below 5 years with pneumococcal meningitis and found that focal neurological deficits (motor impairment) were present in 8 children (14%) at discharge. In 7 of them, matching cerebral lesions were identified by neuroimaging: cerebral infarction in five children, cerebral vasculitis and cerebral abscess in one child each.[24]

In low-income countries, cohort studies specifically on pneumococcal meningitis are lacking and data could be derived from clinical trials only. In a double-blind, placebo-controlled trial among 238 children with pneumococcal meningitis in Malawi, focal neurological deficits after discharge were subdivided in hemiplegia, cerebral palsy, speech disorder and motor delay, and were identified in 3 (1%), 15 (6%), 2 (1%) and 9 (4%) patients, respectively.[25] Adjunctive dexamethasone treatment was given in 307 of 598 (55%) children, and did not affect the proportion of neurological sequelae. In this clinical trial, focal neurological deficits occurred less often after meningococcal meningitis as compared to pneumococcal meningitis: a speech disorder was identified in two of 67 (3%) children, and one child had cerebral palsy.[25] In Brazil, a prospective cohort study of children with meningococcal meningitis described focal neurological deficits in 2 of 68 children (3%).[10] In a study among 157 children after an epidemic of group A meningococcal meningitis in rural West Africa, 2% had focal neurological deficits during follow-up 6–12 months after meningococcal meningitis.[9] Interestingly, among children surviving meningitis, studies showed no difference in occurrence of focal neurological deficits between high-resource countries and low-resource countries (see Tables 1 and 2).

Adults

A prospective nationwide cohort study in the Netherlands including 696 adults with culture-proven community-

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