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Neurological sequelae remain frequent after bacterial meningitis in children

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Abstract

Aim: To examine the incidence, clinical presentation and risk factors for neurological sequelae following childhood community-acquired bacterial meningitis (CABM).

Methods: We included all children aged 1 month to 15 years old with CABM in North Denmark Region, 1998-2016. Using medical records, we registered baseline demographics, signs and symptoms at admission, laboratory investigations, and outcome assessed by the

Glasgow Outcome Scale (GOS). A GOS score of 1-4 was considered an unfavourable outcome. We used modified Poisson regression to examine predefined risk factors for neurological sequelae among survivors.

Results: We identified 88 cases of CABM in 86 patients (45 female) with a median age of 1.4 years (interquartile range 0.7-4.6). *Neisseria meningitidis* was the most common pathogen (48/88). Neurological sequelae occurred in 23 (27%) as hearing deficits in 13 (15%), cognitive impairment in 10 (12%), and paresis or sensory deficits in 8 (9%). Unfavourable outcome was observed in 16 (18%) patients and three (3%) patients died. Abnormalities on cranial imaging remained the only independent risk factor for developing neurological sequelae in adjusted analysis.

Conclusion: Neurological sequelae following CABM in children remain frequent and abnormal cranial imaging may be an independent risk factor.

Key notes:

- In this retrospective population-based cohort study, the risk of neurological sequelae following community acquired bacterial meningitis in children remained high (27%) in spite of general improvements in medical care.
- The most frequent sequelae among survivors were hearing deficits (15%) followed by cognitive impairment (12%), and motor or sensory deficits (9%).
- Serious complications diagnosed on cranial imaging may be an independent risk factor for long-term neurological sequelae.

Keywords: bacterial meningitis, dexamethasone, long-term sequelae, neurological impairment, risk factors.

Introduction

Despite improvements in general medical care, community-acquired bacterial meningitis (CABM) in children remains a severe disease with a case fatality rate of 3 to 7% and a high risk of neurological sequelae (16-50%) (1-5). The pathophysiology of CABM involves inflammation of the blood-brain barrier, loss of vascular autoregulation, increased intracranial pressure, and brain oedema (6). This may lead to damage of neurons and ultimately neurological deficits (6). Hydrocephalus may result both from impaired resorption of cerebrospinal fluid (CSF) by arachnoid villi and obstructed flow at the level of third or fourth ventricle (7-9).

A meta-analysis of outcome following childhood CABM found hearing deficit to be the most common neurological sequela (11%) followed by paresis (4%), seizures (4%) and mental retardation (4%) (3). The risk of hydrocephalus has been reported to be less than 3% (4). The increased risk of long-term developmental, learning and behavioural difficulties may eventually result in lower educational achievement and reduced capability of economic self-sufficiency in adult life (10-12). However, changes in bacterial aetiology after the implementation of childhood vaccination programmes and general improvements in medical care may have reduced risks of serious complications of childhood CABM.

Thus, we set out to examine the incidence, clinical characteristics, and pre-defined risk factors for neurological sequelae following childhood CABM in North Denmark Region from 1998 through 2016.

Material and methods

Setting and study population

We conducted a retrospective population-based cohort study of children with CABM from 1st of January 1998 to 1st of February 2016 in North Denmark Region. Healthcare is tax-financed in Denmark and free of charge at the point of delivery for all residents.

The catchment population increased from 493,298 in 1998 to 585,499 inhabitants in the first quarter of 2016 mainly due to an administrative reform (13). Throughout the study period,

two paediatric departments provided acute care for all children below 15 years of age and the Department of Clinical Microbiology at Aalborg University Hospital was responsible for all microbiological analyses in the region. The department has also kept track of samples sent for supplementary analyses at Statens Serum Institut (Copenhagen). Patients with CABM were identified in the laboratory information system (ADBakt, Autonik, Sweden) at the Department of Clinical Microbiology.

Patients were included if they were between 1 month and 15 years of age, had symptoms and signs suggesting CABM and ≥ 1 of the following criteria were fulfilled:

1. Positive cerebrospinal fluid (CSF) culture (n=84).
2. Positive blood culture and one or more of the following CSF findings: > 10 leukocytes/mL; CSF:blood glucose ratio< 0.23; CSF glucose < 1.9 mmol/L; protein > 2.2 g/L (n=2).
3. Detection of bacteria in Gram stain of CSF (n=0).
4. Non-culture detection of bacteria in CSF by either antigen test or polymerase chain reaction for bacterial DNA (n=2).

Only the strongest criterion was noted (1>2>3>4). Exclusion criteria were:

1. Previous ventriculo-peritoneal (VP) shunt or external ventricular drainage.
2. Hospital-acquired bacterial meningitis defined by the Centers for Disease Control and Prevention (14).
3. Primary brain abscess.

Brain abscess was categorised as primary if it was diagnosed within the first few days of admission and secondary if it developed during admission preceded by cranial imaging without brain abscess at admission.

Patient Data

Data collection was performed until December 2016 using all available information in the hospital records. We accessed the medical records to obtain information on baseline demographics, signs and symptoms at admission and laboratory data. The radiologists' conclusions were used for results of cranial imaging (Table 1). Neuroradiological complications were defined as presence of newly acquired hydrocephalus, brain infarction or haemorrhage, sinus thrombosis, brain oedema, hygroma, subdural empyema, brain herniation, or secondary brain abscess. Patients were categorised according to Paediatric Glasgow Coma Scale (PGCS) at admission. However, PGCS was often missing in the records and therefore we constructed an estimated PGCS (ePGCS) based upon available information: Coma, need for intubation to protect airways (1 point), moderately to severely altered mental status, intubation not required (2 points), mildly altered mental status (3 points), and normal mental status (4 points).
For children >2 months of age, dexamethasone was added to the local treatment guideline (cefotaxime and penicillin G) in year 2015.

Long-term neurological sequelae were defined as persistent deficits after discharge, *e.g.* hearing deficits with or without cochlear implant, cognitive impairment, motor or sensory nerve deficits, hydrocephalus, seizure disorder, and aphasia. Cognitive impairment was defined as any patient requiring inter-disciplinary follow-up for learning difficulties, behavioural problems, or short-term memory deficits at the Department of Pediatrics. Seizure disorder was defined as children registered with seizures or receiving prophylactic anti-epileptic drugs during follow-up with exclusion of patients who stopped such treatment at first routine outpatient visit after CABM. Follow-up time ranged from 10 months to 16 years (only one patient had less than 12 months follow-up time).
We also used the Glasgow Outcome Scale (GOS) to assess outcomes: Death (1 point), vegetative state (2 points), severe disability, dependent on others for activities of daily living (3 points), moderate disability, independent in daily living but with neurological deficit making

the person unable to return to school (4 points), no significant disability and resumption of normal daily life (5 points) (15). A GOS score of 1-4 was considered an unfavourable outcome.

Statistical analyses

Categorical variables were described as proportions with percentages and compared with Fisher's exact test due to the low numbers in each cell (16). Continuous variables were described as medians with interquartile ranges (IQR) and compared with the Mann-Whitney's U-test. A two-tailed p-value< 0.05 was considered statistically significant. We computed incidence rates (IRs) with 95% confidence intervals (95% CI) as the annual number of cases with CABM divided by the corresponding North Denmark population <15 years of age by 1st of January each year. Next, we compared incidence rates through the study period by direct standardisation using the distribution of children by January 1st 2016 as reference.

We used multivariable modified Poisson regression analyses using the robust sandwich estimator to examine adjusted relative risks with 95% CIs for predictors of neurological sequelae among survivors. The number of events (n=23) restricted the number of variables included in the model. Since there was no substantial differences in age or sex of patients with neurological sequelae compared with those without such complications, we chose to include the following variables based on previous studies and clinical relevance: Pneumococcal aetiology (yes/no), neuroradiological complications (yes/no), and adjunctive dexamethasone treatment (yes/no) (3,4,17,18,19). STATA MP® version 15.1 was used for all for statistical analyses.

Ethical considerations

The Study was notified to the North Denmark Region in accordance with a directive from the Danish Data Protection Agency (2008-58-0028). Approval from the local Ethics Committee

or the Danish Board of Health was not required for this type of study in Denmark at the time the study was conducted.

Results

We identified 88 episodes of CABM in 86 children during 1,951,306 person-years of observation corresponding to an overall mean standardised incidence rate of 4.39 (95% CI 2.95-5.83) per 100,000 person-years (Figure 1). The incidence decreased from 5.8 (95% CI 1.1-10.5) to 1.0 (95% CI 0-2.9) per 100,000 person-years during the study period. The median age at diagnosis was 1.4 years (IQR 0.7-4.6) and 45 (51%) were females (Table 1). At admission fever was present in 82/87 (94%), neck stiffness in 39/81 (48%), petechiae in 39/84 (46%), and impaired mental status in 57/88 (65%). Laboratory results showed a median C-reactive protein 112 mg/L (IQR 55-206) and a median CSF leukocyte count of 1,325 10^6/L (IQR 85-4050). *Neisseria meningitidis* (55%) and *Streptococcus pneumoniae* (35%) were the most common pathogens followed by *Streptococcus agalactiae* (5%) (Table 2).

Abnormalities on cranial imaging were seen in 11 out of 29 scanned patients (33%). The most common findings were hydrocephalus in five, infarction in four, and generalised oedema and hygroma in three each. Empiric adjunctive dexamethasone was administered to 8/88 (9%) patients, and 49/88 (56%) were admitted at the paediatric intensive care unit at Aalborg University Hospital. We observed an unfavourable outcome at discharge in 16/88 (18%) patients and a case fatality rate of 3/88 (3%).

Neurological sequelae occurred in 23 (27%) out of 85 surviving cases with hearing deficit as the most common 13/85 (15%) (Table 3). Cognitive impairment (including learning difficulties, behavioural problems and short-term memory loss) was found in 10/85 (12%), motor or sensory nerve deficits in 8/85 (9%), and seizure disorder in 6/85 (7%). Hydrocephalus was diagnosed in 5/85 (6%) and aphasia in 4/85 (5%) patients. A few

patients diagnosed with epilepsy stopped prophylactic anti-epileptic drugs during the study period without any new seizures registered in the medical records at end of follow-up.
In univariate analysis of risk of long-term neurological sequelae, we found that predisposing infection, abnormal cranial imaging, pneumococcal aetiology, and seizures during admission were more frequent among patients with long-term neurological sequelae than among those without such complications (Table 4). Similar comparisons in multivariable analyses yielded adjusted RRs of 3.49 (95% CI 1.99-6.14) for abnormalities on cranial imaging, 1.66 (95% CI 0.73-3.79) for pneumococcal aetiology, and 0.84 (95% CI 0.34-2.08) for use of adjunctive dexamethasone.

Discussion

In our study of childhood CABM patients with virtually complete follow-up, we found that long-term neurological sequelae occurred in 27% of survivors with hearing deficits as the most common sequela. Abnormal cranial imaging, pneumococcal aetiology and seizures during admission were more frequent among patients with long-term neurological sequelae compared with patients without such complications, but only abnormal cranial imaging remained an independent risk factor in multivariable analysis.

Despite general improvements in medical care and decreased case-fatality of childhood CABM, risk of long-term neurological sequelae following CABM has not decreased markedly over time (20). Compared with our study, a meta-analysis of studies from 1980 to 2008 reported lower risks of overall long-term neurological sequelae (20% vs. 27%) as well as hearing deficits (8% vs. 15%) (4). Of note, meningitis caused by *S. pneumoniae* was more frequent and *Haemophilus influenzae* less frequent in our cohort than in the meta-analysis and differences in their associated prognosis may partly explain these observations (3,4).

In our study, abnormal cranial imaging (any new diagnoses of brain infarction, hydrocephalus, abscess, and empyema) was a significant risk factor of neurological sequelae in childhood CABM. However, the observed association between abnormal cranial MRI and neurological sequelae may partly represent confounding by indication leading to an overestimation of measures of risk. Still, the findings consisted of major abnormalities such as hydrocephalus, infarction, generalised oedema, hygroma, haemorrhage, cerebral herniation, and brain abscess, which are known to cause serious sequelae. Even though a large systematic review of published studies of childhood meningitis from 1960 until 2009 did not address abnormal cranial imaging as a risk factor (21), our results are in line with other recent reports showing an association between brain infarctions or hydrocephalus and increased risk of long-term neurological sequelae (17,18).

Pneumococcal aetiology was also associated with an increased risk of long-term neurological sequelae in our study, although the width of the 95% CI leaves room for interpretation of significance. However, as this association is in accordance with previous studies and may be related to bacterial virulence factors, host inflammatory response, and a predilection of *S. pneumoniae* for causing brain infarctions (3,4,17,22,23,24,25) we believe that limited sample size is the main reason for this statistical uncertainty.

The use of adjunctive dexamethasone in childhood CABM is controversial. A Cochrane database systematic review of corticosteroids in childhood CABM showed a significant reduction in risk of hearing loss in *H. influenzae* meningitis, while the effect in meningitis caused by other pathogens was more uncertain (19). In our study, we did not observe a significant association between dexamethasone treatment and improved outcome. However, dexamethasone was not implemented before year 2015 in local guidelines for management of bacterial meningitis in children above two months of age and only eight patients received this treatment in our study.

Based on previous studies and our results, we suggest that patients with pneumococcal meningitis or abnormalities on cranial imaging should receive careful evaluation during follow-up for timely diagnosis of possible neurological sequelae and rehabilitation.

Evaluations of effects of implementation of adjunctive dexamethasone in large contemporary cohorts of childhood meningitis are sparse and further improvement in prognosis of bacterial meningitis is desperately needed. Although difficult to implement in clinical research at this stage, areas of potential interest could be additional anti-inflammatory treatments (26), non-bacteriolytic antibiotic therapy (27) and management bundles for increased intracranial pressure in patients with pneumococcal meningitis (28).

Inherent limitations of the retrospective design of our study include incompleteness of data as well as non-standardised diagnostic work-up and room for adjusting treatment by attending physicians providing care for the patients. Of relevance, cranial imaging was not performed in all patients but important abnormalities would most likely have resulted in symptoms requiring further diagnostic examinations during admission or follow-up. Outpatient follow-up is paramount for analysing long-term sequelae, and a previous study observed spontaneous resolution of neurologic complications within one year following childhood CABM (29). In Denmark, all serious complications in children are treated and followed in outpatient hospital settings (30), and the long observation period in our study enabled us to track and document such serious sequelae. However, some patients may have had minor sequelae not affecting cognitive development or everyday physical abilities that were cared for by their general practitioner, which would lead to an underestimation of the overall proportion with neurological sequelae.

In conclusion, we observed a persistent high risk of long-term neurological sequelae among survivors of childhood CABM with hearing deficits as the most common sequela. Our results suggest that serious complications diagnosed on cranial imaging may be an independent risk factor for long-term neurological sequelae.

List of abbreviations:

CABM = community-acquired bacterial meningitis

PGCS = paediatric Glasgow Coma Scale

ePGCS = estimated paediatric Glasgow Coma Scale

GOS = Glasgow Outcome Scale

Conflicts of Interest and funding:

None.

References:

1. Nigrovic LE, Kuppermann N, Malley R. Children with bacterial meningitis presenting to the emergency department during the pneumococcal conjugate vaccine era. *Acad Emerg Med* 2008; 15: 522–8.
2. Thigpen MC, Whitney CG, Messonnier NE, Zell ER, Lynfield R, Hadler JL, et al. Bacterial meningitis in the United States, 1998-2007. *N Engl J Med* 2011; 364: 2016–25.
3. Baraff LJ, Lee SI, Schriger DL. Outcomes of bacterial meningitis in children: a meta-analysis. *Pediatr Infect Dis J* 1993; 12: 389–94.
4. Edmond K, Clark A, Korczak VS, Sanderson C, Griffiths UK, Rudan I. Global and regional risk of disabling sequelae from bacterial meningitis: a systematic review and meta-analysis. *Lancet Infect Dis* 2010; 10: 317–28.
5. Chandran A, Herbert H, Misurski D, Santosham M. Long-term sequelae of childhood bacterial meningitis: an underappreciated problem. *Pediatr Infect Dis J* 2011; 30: 3–6.
6. Lepage P, Dan B. Infantile and childhood bacterial meningitis. *Handb Clin Neurol* 2013; 112: 1115–25.
7. 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.
8. Mactier H, Galea P, McWilliam R. Acute obstructive hydrocephalus complicating bacterial meningitis in childhood. *BMJ* 1998; 316: 1887–9.
9. Kasanmoentalib ES, Brouwer MC, van der Ende A, van de Beek D. Hydrocephalus in adults with community-acquired bacterial meningitis. *Neurology* 2010; 75: 918–23.
10. Dodge PR, Swartz MN. Bacterial meningitis – A review of selected aspects. II. Special neurologic problems, postmeningitic complications and clinicopathological correlations. *N Engl J Med* 1965; 272: 1003–10.
11. de Louvois J, Halket S, Harvey D. Effect of meningitis in infancy on school-leaving examination results. *Arch Dis Child* 2007; 92: 959–62.

12. Roed C, Omland LH, Skinhoj P, Rothman KJ, Sorensen HT, Obel N. Educational achievement and economic self-sufficiency in adults after childhood bacterial meningitis. *JAMA* 2013; 309: 1714–21.
13. Statistics Denmark. Available from: http://www.statistikbanken.dk/10021. Accessed January 27, 2019.
14. Garner JS, Jarvis WR, Emori TG, Horan TC, Hughes JM. CDC definitions for nosocomial infections, 1988. *Am J Infect Control* 1988; 16: 128–40.
15. Jennett B, Teasdale G, Braakman R, Minderhoud J, Knill-Jones R. Predicting outcome in individual patients after severe head injury. *Lancet* 1976; 1: 1031–4.
16. Warner P. Testing association with Fisher's Exact test. *J Fam Plan Reprod Heal care* 2013; 39: 281–4.
17. Chang C-J, Chang W-N, Huang L-T, Chang Y-C, Huang S-C, Hung P-L, et al. Cerebral infarction in perinatal and childhood bacterial meningitis. *QJM* 2003; 96: 755–62.
18. Bargui F, D'Agostino I, Mariani-Kurkdjian P, Alberti C, Doit C, Bellier N, et al. Factors influencing neurological outcome of children with bacterial meningitis at the emergency department. *Eur J Pediatr* 2012; 171: 1365–71.
19. Brouwer MC, McIntyre P, Prasad K, van de Beek D. Corticosteroids for acute bacterial meningitis. *Cochrane database Syst Rev* 2015; 9: CD004405.
20. Sáez-Llorens X, McCracken GH. Bacterial meningitis in children. *Lancet* 2003; 361: 2139–48.
21. de Jonge RCJ, van Furth AM, Wassenaar M, Gemke RJBJ, Terwee CB. Predicting sequelae and death after bacterial meningitis in childhood: a systematic review of prognostic studies. *BMC Infect Dis* 2010; 10: 232.
22. Oostenbrink R, Maas M, Moons KGM, Moll HA. Sequelae after bacterial meningitis in childhood. *Scand J Infect Dis* 2002; 34: 379–82.
23. Quagliarello V, Scheld WM. Bacterial meningitis: pathogenesis, pathophysiology, and progress. *N Engl J Med* 1992; 327: 864–72.

24. Chang YC, Huang CC, Wang ST, Chio CC. Risk factor of complications requiring neurosurgical intervention in infants with bacterial meningitis. *Pediatr Neurol* 1997; 17: 144–9.
25. Arditi M, Mason EO, Bradley JS, Tan TQ, Barson WJ, Schutze GE, et al. Three-year multicenter surveillance of pneumococcal meningitis in children: clinical characteristics, and outcome related to penicillin susceptibility and dexamethasone use. *Pediatrics* 1998; 102: 1087–97.
26. Mook-Kanamori BB, Geldhoff M, van der Poll T, van de Beek D. Pathogenesis and pathophysiology of pneumococcal meningitis. *Clin Microbiol Rev* 2011; 24: 557–91.
27. Spreer A, Lugert R, Stoltefaut V, Hoecht A, Eiffert H, Nau R. Short-term rifampicin pretreatment reduces inflammation and neuronal cell death in a rabbit model of bacterial meningitis. *Crit Care Med* 2009; 37: 2253–8.
28. Lindvall P, Ahlm C, Ericsson M, Gothefors L, Naredi S, Koskinen L-OD. Reducing intracranial pressure may increase survival among patients with bacterial meningitis. *Clin Infect Dis* 2004; 38: 384–90.
29. Pomeroy SL, Holmes SJ, Dodge PR, Feigin RD. Seizures and other neurologic sequelae of bacterial meningitis in children. *N Engl J Med* 1990; 323: 1651–7.
30. Olejaz M, Juul Nielsen A, Rudkjøbing A, Okkels Birk H, Krasnik A, et al. Denmark health system review. *Health Syst Transit* 2012; 14: 1–192.

Table 1: Clinical characteristics at admission of children with community-acquired bacterial meningitis in North Denmark Region, 1998-2016.

Characteristics	n/N (%) or median (IQR)
Age, years (median, IQR) (n=88)	1.4 (0.7-4.6)
Females	45/88 (51)
Pre-disposing infection*	18/88 (20)
Duration of symptoms, (days) (n=87)	2 (1-4)
Headache	22/36 (61)
Nausea/vomiting	67/74 (91)
Phono-photophobia	5/73 (7)
Neck stiffness	39/81 (48)
Petecchiae	39/84 (46)
Fever (>37.9°C)	82/87 (94)
ePGCS	
1	3/88 (3)
2	20/88 (23)
3	34/88 (39)
4	31/88 (35)
Motor or sensory nerve deficits	2/37 (5)
Cranial nerve palsy	3/35 (9)
Seizures before admission	13/81 (16)
C-reactive protein (mg/L) (n=88)	112 (55-206)
B-leukocytes (10^9/L) (n=88)	18 (12-26)
Thrombocytes (10^9/L) (n=81)	306 (201-379)
P-creatinine (µmol/L) (n=85)	38 (27-52)
CSF leukocytes (10^6/L) (n=86)	1325 (85-4050)
CSF erythrocytes (10^6/L) (n=83)	70 (15-313)
CSF glucose (mmol/L) (n=84)	2.6 (0.4-3.9)
CSF/plasma glucose index (n=79)	0.41 (0.07-0.61)
CSF protein (g/L) (n=87)	1.1 (0.30-2.0)
CSF culture detection of pathogen**	86/88 (98)
Blood culture positive	48/88 (55)
Cranial imaging during admission	29/88 (33)
Cranial imaging abnormalities***	11/29 (38)
Adjunctive dexamethasone treatment	8/88 (9)
Intensive care unit admission	49/88 (56)

ePGCS: estimated paediatric Glasgow Coma Scale. CSF: Cerebrospinal fluid.

*Acute otitis media in 11, sinusitis in four, pneumonia in three, mastoiditis in none.

** Includes patients diagnosed by CSF culture (n=84) and by bacterial DNA or antigen detection (n=2).

***Hydrocephalus in five, infarction in four, generalised oedema in three, hygroma in three, haemorrhage in two, cerebral herniation and secondary brain abscess in one each.

Table 2: Bacterial aetiologies of community-acquired bacterial meningitis in children in North Denmark Region, 1998-2016.

Pathogen	**N=88 (%)**
Neisseria meningitidis	48 (55)
Streptococcus pneumoniae	31 (35)
Streptococcus agalactiae (haemolytic group B streptococcus)	5 (5)
Haemophilus influenzae	3 (3)
Listeria monocytogenes	1 (1)

Table 3: Outcome of community-acquired bacterial meningitis in children in North Denmark Region, 1998-2016.

Outcome	**N=88 (%)**
Glasgow Outcome Score at discharge	
1	3 (3)
2	0
3	5 (6)
4	8 (9)
5	72 (82)
Long-term sequelae	**N=85 (%)**
Overall	23 (27)
Hearing deficits	13* (15)
Cognitive impairment	10 (12)
Motor or sensory nerve deficits	8 (9)
Seizure disorder	6 (7)
Hydrocephalus	5 (6)
Aphasia	4 (5)

*Includes two patients with cochlear implant. Hearing loss was observed among 7/24 (23%) of patients with pneumococcal meningitis vs. 6/57 (11%) of other meningitis patients (p=0.21).

Table 4: Comparison of patients with long-term sequelae vs. patients without long-term sequelae among the 85 survivors of community-acquired bacterial meningitis in North Denmark Region, 1998-2016.

	Long-term sequelae (n=23)	**No long-term sequelae (n=62)**	**p-value**
Age (years)	1.0 (0.4-4.0)	1.5 (0.8-6.1)	0.11
Female	10 (43)	34 (55)	0.47
Predisposing infection	9 (39)	8 (13)	0.01
Duration of symptoms (days)	3 (2-4)	2 (1-3)	0.08
Seizures at admission	4 (17)	9 (15)	0.74
Impaired mental state (ePGCS<4)	19 (83)	36 (58)	0.04
Pneumococcal aetiology	14 (61)	16 (26)	0.004
C- reactive protein (mg/L)	106 (38-209)	116 (61-203)	0.56
CSF leukocytes (10^6/L)	647 (152-2870)	1824 (92-6100)	0.51
CSF:plasma glucose ratio	0.2 (0.02-0.54)	0.44 (0.18-0.65)	0.11
CSF protein (g/L)	1.4 (0.8-2.9)	1.1 (0.3-1.8)	0.18
Dexamethasone	2 (9)	6 (10)	1.00
Cranial imaging performed	12 (52)	17 (26)	0.04
Pathological findings on cranial imaging (yes/no)	9 (39)	0	<0.001
Seizures during admission	11 (48)	14 (23)	0.03
Intensive care unit admission	15 (65)	31 (50)	0.23

Figure 1 legend:

*Excludes patients 0-30 days of age.

Figure 1: Incidence rates of childhood community-acquired bacterial meningitis in North Denmark Region from 1998 through 2016.