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Predictors for Neurologic Complications of Bacterial Meningitis in Children in Kosovo

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Abbreviations: M, Mortality; CSF, Cerebrospinal fluid; RR, Relative risk; CI, Confidence interval.

Abstract

Aim. To identify predictors for neurologic complications in pediatric patients with bacterial meningitis.

Material and Methods. Our study was observational and retrospective. Fifteen potentially relevant predictors were chosen to analyze their association with the incidence of neurologic complications. The relative risk and 95 percent confidence interval was used to quantify the strength of these associations.

Results. Of the 277 children who were treated for bacterial meningitis, neurologic complications developed in 60 patients (22%) and 15 children died, yielding an overall mortality rate of 5%. The most important predictors for neurologic complications in pediatric patients with bacterial meningitis were pre-hospital seizures and their recurrence >24 hours after admisssion (RR 6.7 and RR 6.2, 95% CI), a large decrease in CSF leukocyte count (<100 cells/mm^3) after 48 hours (RRs 4.0, 95% CI), age less than 12 months (RR 3.7, 95% CI), the presence of neurologic deficit (RR 3.3, 95% CI) and altered mental status (RR 2.7, 95% CI).

Conclusions. The occurrence of seizures, a large decrease in CSF leukocyte count after 48 hours and age less than 12 months have been identified as the strongest predictors for neurologic complications of bacterial meningitis in children and may be of value in selecting patients for more intensive therapy.

Introduction

Bacterial meningitis is an emergent disease that has a high mortality rate and is associated with neurologic complications, even if treated early. Despite the development of antibiotics that are more effective at treating bacterial meningitis, the mortality rates continue to be high, ranging between 5 and 30% [1-7]. The risk of developing complications or dying has been shown to be related to the age and underlying health status of the patient, the causative pathogen, the severity and duration of illness at the time of presentation, and to delays in the initiation of antibiotic therapy [1]. The neurologic complications that occur from bacterial meningitis in children can develop at any time during the course of bacterial meningitis but some of them can persist as long-term complications such as; hearing loss, seizures, hemiplegia, neuropsychological impairment and developmental disabilities. The neurologic complications that can develop during the course of bacterial meningitis include: 1) subdural effusions or empyemas; 2) cerebritis; 3) cerebral abscesses; 4) hydrocephalus; 5) focal neurological deficits (e.g., hearing loss, cranial nerve palsies, hemiparesis, or

quadriparesis); 6) cerebrovascular abnormalities; 7) altered mental status; 8) seizures. Of these, altered mental status and seizures are more likely seen during the acute phase of the illness (rather than as a long-term complication) [4, 8-10].

The aim of the study was to identify predictors for neurological complications of bacterial meningitis in children in Kosovo.

Material and Methods

Our study was observational and retrospective. We included 277 children <16 years of age (males 162 cases, females 115 cases),treated for BM at the Infectious Diseases Clinic in Prishtina (Kosovo) during a six year period (1997-2002). A "case" of bacterial meningitis was defined as any patient <16 years of age who was treated for probable or confirmed bacterial meningitis according to the World Health Organization criteria: clinical symptoms (e.g. fever, meningeal signs) and changes in cerebrospinal fluid (CSF): pleocytosis (>100 mm^3) and either *direct* (positive blood or CSF culture) or *indirect* (positive latex agglutination test or CSF Gram stain) confirmation of bacterial presence. Children who didn't fulfill the criteria for "a case of bacterial meningitis" were excluded from the study.

Fifteen potentially relevant predictors were chosen to analyze their association with the incidence of neurologic complications of bacterial meningitis in children treated in our ward. The relative risk and 95 percent confidence interval was used to quantify the strength of these associations. There were no missing data on 15 variables collected from the medical records including: 1) age (which was later categorized into specific age groups); 2) gender; 3) demographic data (i.e., whether the patient lived in an urban or a rural community); 4) whether or not they were hospitalized or treated with antibiotics; 5) the duration of the patient's illness prior to admission; 6) the occurrence of seizures prior to admission; 7) the recurrence of seizures >24 hours after admission; 8) the presence of altered mental status at the time of presentation; 9) the presence of neurological deficits at the time of admission; 10) cerebrospinal fluid (CSF) laboratory parameters; 11) the use of dexamethasone; 12) the use of inotropic agents; 13) the presence/absence of a primary infectious focus; 14) the specific pathogenic agent with which the patient was infected; and 15) whether the patient had a community- or hospital-acquired infection. All children were followed up for 5 years.

Statistical analysis

Data were analyzed using computer program Stata 9.0. The statistical parameters that were analyzed included structure index, mean, and standard deviation. The relative risk (RRs) and 95 percent confidence interval was calculated for predictors that were found to be associated with an increased risk of neurologic complications. The distribution of patient characteristics between the different groups was compared using the χ^2-test for discrete data and the t-test and one-way ANOVA for parametric data. All p-values <0.05 were considered to be statistically significant.

Results

Of the 277 children who were treated for bacterial meningitis, neurological complications developed in 60 patients (22%) and 15 children died, yielding an overall mortality rate of 5%. The highest mortality rate was observed in neonates (RRs 19.3) and children <12 months of age had the highest incidence of neurologic complications (RRs 3.7) (Table 1).

Table 1: The outcome of BM according to age group.

Age group	n	% of study sample	Patients with NCs (n)	%	Deaths (n)	%
0-1 months	7	3	1	14	5	71
2-11 months	108	39	42	39	8	7
1-2 years	37	13	7	19	1	3
3-5 years	56	20	4	7	-	-
6-10 years	45	16	2	4	1	2
11-16 years	24	9	4	17	-	-
Total	277	100	60	22	15	5

The neurologic complications observed were: subdural effusion (35/277, 13%), seizures (31/277, 11%), hydrocephalus (7/277, 3%), hearing impairment (3/277, 1%), subdural empyema (2/277, 1%), intellectual impairment (2/277, 1%), spinal abscess (1/277, 0.4%), quadriparesis (1/277, 0.4%), loss of vision (1/277, 0.4%), cerebritis (1/277, 0.4%), subdural hematoma 1/277, 0.4%) and intracerebral hemorrhage 1/277, 0.4%).

Table 2: Incidence of neurological complications and mortality of children with BM, stratified by illness duration (in days) at the time of admission.

Day of illness	n	%	Patients with NCs (n)	%	Deaths (n)	%	Patients without NCs (n)	%
1	83	30	16	19	3	4	64	77
2	60	22	6	10	1	2	53	88
3	45	16	10	22	2	4	33	73
4	27	10	8	30	1	4	18	67
5	22	8	8	36	-	-	14	64
6	5	2	2	40	1	20	2	40
7	19	7	5	26	3	16	11	58
>7	16	6	5	31	4	25	7	44
Total	277	100	60	22	15	5	202	73

The duration of illness at the time of admission was associated with patient outcome (Table 2). The mean duration of illness prior to hospitalization was 2.6 days for patients who recovered without neurologic complications, 3.2 days for patients who survived with neurologic complications, and 5.3 days for patients who died (p<0.01) (Table 3).

Table 3: Average illness duration prior to admission for each patient outcome.

	Patients without NCs	Patients with NCs	Deaths	Total
n	202	60	15	277
(%)	(73%)	(22%)	(5%)	(100%)
Average duration of illness prior to admission, days	2.6	3.2	5.3	3.7
One way ANOVA	F=66.2, p<0.001			

A total of 188 patients were admitted during the first 3 days of their illness. A lower incidence of neurologic complications was recorded in this group as compared to the patients who were admitted after at least three days of illness. The observed differences were statistically significant (RRs 1.9, 95% CI respectively; p<0.001) (Table 4).

Table 4: Association between various clinical factors and the development of neurological complications in children with bacterial meningitis.

Prognostic factor	n	NCs	%	Relative risk (95% CI)
Seizures prior to admission	60	39	65	6.7 (4.45 – 9.96)
Recurrent seizures >24 h after admission	41	31	76	6.2 (4.32 – 8.06)
Dexamethasone use	243	58	24	4.1 (1.22 – 14.92)
Large decrease in CSF pleocytosis (<100cells/mm^3) after 48 hours	22	12	54	4.0 (1.83-8.88)
Age <12 months old	108	42	39	3.7 (2.26 – 5.98)
Neurological deficit at the time of admission	44	23	52	3.3 (2,17 – 4,73)
Altered mental status	141	44	31	2.7 (1.60 – 4.48)
Turbid CSF after 48 hours	23	9	39	2.2 (0.98-4.75)
Recurrence of fever lasting >48 hours	140	53	38	2.1 (1.78-2.59)
Use of inotropic agents	32	12	37	1.9 (1.11 – 3.03)
Admission after three days of illness	89	28	31	1.9 (1.19 – 2.85)
Previously treated with antibiotics	100	26	26	1.4 (0.86 – 2.10)
Previously hospitalized	87	22	25	1.3 (0.79 – 1.98)
Patients with a primary focus of infection	183	43	23	1.3 (0.80 – 2.17)
Female gender	115	27	23	1.2 (0.74 – 1.80)
Rural location of residence	161	36	22	1.1 (0.69 – 1.71)

Children who had seizures prior to admission (n=60, RR 6.7) and those who had recurrence of seizures >24 hours after admission were found to be at increased risk for developing neurologic complications (n=41; RRs 6.2).

Also children who were admitted with an altered mental status (n=141; RR 2.7) and those who had neurologic deficits at the time of admission (n=44; RRs 3.3) were found to be at increased risk for developing neurologic complications.

Dexamethasone was used in 243 patients. The incidence of neurologic complications and mortality were higher in patients who were treated with dexamethasone use compared to those who were not treated with dexamethasone (RRs 4.1 and 2.0).

Inotropic agents were used in 32 patients and in this group was recorded a higher incidence of neurologic complications as compared to patients in whom inotropic agents were not used (RRs 1.9).

A lower CSF:blood glucose ratio was found in patients who died (0.21) and in those who developed neurologic complications (0.26) as compared to those who were cured and did not develop neurologic complications (0.34). The highest mean protein levels (3.0 g/L) were found in patients who manifested neurologic complications as compared to patients who were cured without neurologic complications (2.3 g/L) or patients who died (1.3 g/L).

CSF samples from the second LP, which was performed 48 hours after the initiation of antimicrobial therapy, remained turbid in 23/262 cases; 9 patients developed neurological complications and 2 patients died. (RRs 2.1 and 2.4).

A higher incidence of neurologic complications (54%) was recorded in children who had a large decrease in pleocytosis (<100 cells/mm^3)(n=22) in the CSF samples from the second LP performed 48 hours after admission (n=262) (RRs 4.0).

Recurrence of fever lasting >48 hours was recorded in 140 patients. A higher incidence of neurologic complications was recorded in these patients as compared to cases who did have fever lasting >48 hours (RR 2.1).

Patients who had hospital-acquired infections, although it was a small number of patients (n=20), had a higher mortality rate (3 patients died) compared to patients who had community-acquired infections (n=257) (12 patients died) (RRs 3.2). Neurologic complications developed more frequently in patients with community-acquired infections (RRs 4.59).

The three most common pathogens that were isolated in the included children were *N. meningitidis* (71 cases), *H. influenzae* (22 cases), and *S. pneumoniae* (17

cases). Neurologic complications developed more frequently in patients who were infected with *H. influenzae* (11 cases) than in patients who were infected with *S. pneumoniae* (5 cases) or *N. meningitidis* (15 cases). Of the 71 patients who had meningococcal meningitis one died, whereas no deaths were reported for patients who were infected with *S. pneumoniae* or *H. influenzae*. Gram negative bacilli were isolated in 11 cases; 3 cases developed neurologic complications and 1 died.

Previous hospitalization (n=87, RR 1.3), previous treatment with antibiotics (n=100, RR 1.4), turbid CSF on admission (n=245, RR 1.0), leukocytopenia (<4 000 white blood cells per microliter) on admission (n=50, RR 1.4), presence of primary focus of infection (n=183, RR1.1) gender and rural location of residence were not found to be associated with increased risk for developing neurologic complications of bacterial meningitis in children.

Discussion

Bacterial meningitis is still a common disease in Kosovo. During the years of our study the annual incidence of bacterial meningitis was 2.8 cases per 100.000 popullation and it was higher from the last previously reported in Kosovo (2.3 cases per 100.000 popullation). About 81% of cases in all ages (340 cases) occured in children while 75% of pediatric bacterial meningitis cases occurred in children <5 years of age. Young ages were associated with adverse outcomes; the highest mortality rate was recorded in neonates, and the highest incidence of neurologic complications was found in children who were <12 months of age. Vaccines against meningeal pathogens have not been implemented into national immunization programs in Kosovo. The implementation of *H. influnzae* type b vaccine, universal screening and antibiotic prophylaxis of pregnant women for Group B streptococci and the implementation and availability of the *S. pneumoniae* and *N. meningitidis* conjugate vaccines are the leading factor associated with decreased incidence of bacterial meningitis in countries where routine vaccination is available.

Time required to establish a diagnosis of bacterial meningitis depends on the ability of primary health care services to accurately assess the symptoms and to order immediate patient transfer to specialized institutions in which the promt diagnosis can be confirmed and a suitable antimicrobial therapy can be initiated. Delay in treatment is associated with an increased risk of neurological disability and death [2, 3,10, 20-23]. Aronin SI. Et all. (1998) found that delay in therapy after arrival in the emergency department was associated with adverse clinical outcome when the patient's condition advanced to the highest stage of prognostic severity before the initial antibiotic dose was given [10]. Delayed diagnosis, in this study defined as diagnosis after 3 days of illness, was associated with increased morbidity in survivors.

Numerous studies have sought to identify clinical factors that are associated with adverse outcomes in children with BM [1, 6, 7,11-19, 23]. Klinger G. et all. (2000) found that duration of seizures for >72 hours, presence of coma, use of inotropes, and leukopenia were the most important predictors of adverse outcome [17]. Oostenbrik R. et all. (2002) found that children with bacterial meningitis caused by *Streptococcus pneumoniae* and those with acute focal neurological symptoms tended to have the worst prognosis [15]. Grimwood K . et all. (1996) found that age <= 12 months, tertiary referral, symptoms > 24 h before diagnosis, seizures, focal neurological signs, deteriorating conscious state in hospital, Streptococcus pneumoniae infection and serum sodium concentration < 130 mmol/L were associated with adverse outcomes [19].

In this study, the risk factors associated with statistical significance with the development of neurologic complications include: a decreased level of consciousness, seizures, focal neurological deficits, the duration of illness prior to treatment, age ≤12 months and the use of inotropic agents. Other risk factors identified by previous studies include: alterations in various CSF parameters, delayed sterilization of the CSF, neutropenia, early admission to the intensive care unit, requirement of assisted ventilation, dexamethasone use, the presence of a primary focus of infection, infection caused by *S. pneumoniae* and the presence of underlying disease [5-7,13,15,16,18,19]. Pasquale P. et all. (2007) found that patients with a low CSF cell count, low neutrophils, early admission to ICU or infection by penicillin-nonsusceptible strains of *S. pneumoniae* had an unfavourable outcome more frequently [31].

Alterations in various CSF parameters associated with the development of neurologic complications include low CSF leukocyte count, decreased level of glucose in CSF and elevated CSF protein levels. Tsai MH. et all. (2008) found that CSF leukocyte count ≤200 mm^{-3} (p = 0.013) and protein level ≥330 g l^{-1} (p = 0.022) were significantly risk factors associated with poor outcomes, and physicians should be cautious if such conditions occur [16].

Lebel ML and all.(1989) found that children with

persistently positive cultures had a significantly higher incidence of neurologic abnormalities at the time of hospital discharge (45% *v* 19%) and at followup (41% *v* 13%) and of moderate to profound hearing impairment (35% *v* 15%) than did those with prompt sterilization of CSF [19]. Also in this study children with turbid CSF after 48 hours had higher incidence of neurologic complications (39% *v* 16%) than did those who did not have turbid CSF after 48 hours. A large decrease in the CSF leukocyte count from the second LP was found to be associated with increased incidence of neurologic complications. Patients who manifested recurrence of fever >48 hours after admission and infections caused by *H. influenzae* were found to be associated with increased incidence for neurologic complications.

Previous treatment with antibiotics, previous hospitalization in other hospital words, presence of a primary focus of infection, gender and location of residence (urban/rural location) were not found to be associated with increased incidence for neurologic complications of bacterial meningitis in children in Kosovo.

Many clinical trials were undertaken to determine the effects of adjunctive dexamethasone on outcome in children with bacterial meningitis [23-30]. The results, however, do not point unequivocally to a beneficial effect [30]. Evidence of clinical benefit was strongest for hearing outcomes in children with *H. influenzae* type b meningitis and suggested a protective effect in those with pneumococcal meningitis if the drug was given before or with parenteral antibiotics [24]. In this study adjunctive dexamethasone therapy did not reduce the incidence of neurologic complications and mortality in children with bacterial meningitis.

In conclusion our data indicate that the occurrence of seizures, a large decrease in CSF leukocyte count after 48 hours and age less than 12 months have been the strongest predictors for neurologic complications of bacterial meningitis in children and may be of value in selecting patients for more intensive therapy.

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References

1. Kaplan SL, Woods C. Neurologic complications of bacterial meningitis in children. Curr Clin Top Infect Dis. 1992; 12:37.

2. Quagliarello VJ, Scheld WM. Treatment of bacterial meningitis. N Eng J Med. 1997;336:708-716.

3. Durand ML, Calderwood SB, Weber DJ, et al. Acute bacterial meningitis in adults. A review of 493 episodes. N Eng J Med. 1993;328(1):21-28.

4. Schuchat A, Robinson K, Wenger JD, et al. Bacterial meningitis in the United States in 1995. Active Surveillance Team. New Engl J Med. 1997;337:970–976.

5. Østergaard C, Konradsen HB, Samuelsson S. Clinical presentation and prognostic factors of Streptococcus pneumoniae meningitis according to the focus of infection. BMC Infect Dis. 2005;5:93.

6. van de Beek D, de Gans J, Spanjaard L, et al. Clinical features and prognostic factors in adults with bacterial meningitis. N Engl J Med. 2004;351:1849–1859.

7. McIntyre PB, MacIntyre CR, Gilmour R, Wang H. A population based study of the impact of corticosteroid therapy and delayed diagnosis on the outcome of childhood pneumococcal meningitis. Arch Dis Child. 2005;90:391–396.

8. Kaplan SL, Catlin FI, Weaver T, Feigin RD. Onset of hearing loss in children with bacterial meningitis. Pediatrics. 1984; 73:575-578.

9. Pfister HW, Feiden W, Einhaupl KM. Spectrum of complications during bacterial meningitis in adults. Results of a prospective clinical study. Arch Neurol. 1993;50:575–581.

10. Aronin SI, Peduzzi P, Quagliarello VJ. Community-aquired bacterial meningitis; risk stratification for adverse clinical outcome and effect of antibiotic timing. Ann Inter Med. 1998; 129:862-869.

11. Taylor HG, Mills EL, Ciampi A, et al.The sequelae of Haemophilus influenza meningitis in school-age children. N Engl J Med. 1990;323:1657.

12. Lindberg J, Rosenhall U, Nylen O, Ringnér A. Long-term outcome of Haemophilus influenzae meningitis related to antibiotic treatment. Pediatrics. 1977;60(1):1-6.

13. Schaad UB, Lips U, Gnehm HE, et al. Dexamethasone therapy for bacterial meningitis in children. Lancet. 1993; 342:457-461.

14. Feigin RD, Cutrer WB. Bacterial meningitis beyond the neonatal period. In:Textbook of Pediatric Infectious Diseases, 6th ed., Feigin RD, Cherry JD, Demmler-Harrison GJ, Kaplan SL (Eds). Saunders: Philadelphia, 2009:p.439.

15. Oostenbrink R, Maas M, Moons KG, Moll HA. Sequelae after bacterial meningitis in childhood. Scand J Infect Dis. 2002;34:379–382.

16. Tsai MH, Chen SH, Hsu CY, et al. Pneumococcal menin-

gitis in taiwanese children: Emphasis on Clinical outcomes and prognostic factors. J Trop Pediatr. 2008;54(6):390-394.

17. Klinger G, Chin CN, Beyene J, Perlman M. Predicting the outcome of neonatal bacterial meningitis. Pediatrics. 2000; 106:477-482.

18. Grimwood K, Nolan TM, Bond L, et al. Risk factors for adverse outcomes of bacterial meningitis. J Paediatr Child Health. 1996;32:457-462.

19. Lebel MH, McCracken GH. Jr. Delayed cerebrospinal fluid sterilization and adverse outcome of bacterial meningitis in infants and children. Pediatrics. 1989;83:161-167.

20. Wenger JD, Hightower AW, Facklam RR, Gaventa S, Broome CV. Bacterial meningitis in the United States, 1986: report of a multistate surveillance study. The Bacterial Meningitis Study Group. J Infect Dis. 1990;162:1316–1323.

21. Bohr V, Hansen B, Jessen O, et al. Eight hundred and seventy-five cases of bacterial meningitis. Part I of a three-part series: clinical data, prognosis, and the role of specialised hospital departments. J Infect. 1983;7:21–30.

22. Spanjaard L, Bol P, de Jong MC, Zanen HC. Bacterial meningitis in 366 children in the Netherlands, 1982–1983. Epidemiology and antibiotic therapy. J Antimicrob Chemother. 1986;54:1–8.

23. Akpede GO, Akuhwa RT, Ogiji EO, Ambe JP. Risk factors for an adverse outcome in bacterial meningitis in the tropics: a reappraisal with focus on the significance and risk of seizures. Ann Trop Paediatr. 1999;19:151-159.

24. Girgis NI, Farid Z, Mikhail IA, et al. Dexamethasone treatment for bacterial meningitis in children and adults. Pediatr Infect Dis J. 1989;8:848–851.

25. Odio CM, Faingezicht I, Paris M, et al. The beneficial effects of early dexamethasone administration in infants and children with bacterial meningitis. N Engl J Med. 1991;324:1525–1531.

26. Kennedy WA, Hoyt MJ, McCracken GH Jr. The role of corticosteroid therapy in children with pneumococcal meningitis. Am J Dis Child. 1991;145:1374–1378.

27. Wald ER, Kaplan SL, Mason EO Jr, et al. Dexamethasone therapy for children with bacterial meningitis. Pediatrics.1995;95:21–28.

28. Kilpi T, Peltola H, Jauhiainen T, Kallio MJ. Oral glycerol and intravenous dexamethasone in preventing neurologic and audiologic sequelae of childhood bacterial meningitis. Pediatr Infect Dis J. 1995;14:270–278.

29. Molyneux EM, Walsh AL, Forsyth H, et al. Dexamethasone treatment in childhood bacterial meningitis in Malawi: A randomized controlled trial. Lancet. 2002;360: 211–218.

30. De Louvois J, Blackbourn J, Hurley R, Harvey D. Infantile meningitis in England and Wales: a two year study. Arch Dis Child. 1991;66:603-607.

31. Pagliano P, Fusco U, Attanasio V, et all. Pneumococcal meningitis in childhood: a longitudinal prospective study. FEMS Immunol Med Microbiol. 2007;488-495(8).