

Risk for Childhood Hydrocephalus due to Bacterial Meningitis

Sadie Namani^{1*}, Remzie Koci²

^{1*} Infectious Diseases Clinic, University Clinical Center of Kosovo,
Assistant, Medical Faculty, University of Prishtina, Prishtina, Kosovo

² Pediatric Clinic, University Clinical Center of Kosovo, Prishtina, Kosovo

Abstract

Background: Neurologic complications of childhood bacterial meningitis are encountered frequently, but the risk for childhood hydrocephalus was rarely reported in developing countries.

Aims: The purpose of this study was to analyze the incidence, clinical characteristics and risk factors associated with hydrocephalus in children with bacterial meningitis in developing country Kosovo.

Study design: 354 children treated for bacterial meningitis in the Clinic of Infectious Diseases in Prishtina, Kosovo, were enrolled in the study.

Methods: This study presents retrospective analysis of hydrocephalus cases among children treated for bacterial meningitis in two study periods. In first study period (1997–2002), 277

children and in the second study period (2009–2010), 77 children were prospectively enrolled in the study. The first study period includes years before and after the war in Kosovo (1999). The second study period includes two years study period, a decade after the war in Kosovo.

Results: Of the 277 vs. 77 children, 60 (22%) vs. 33 (43%) patients developed neurologic complications, while there were 15 (5.4%) vs. 2 (2.6%) deaths. Hydrocephalus developed equally in both study periods 7 vs. 2 cases (2.5% vs. 2.6%). Of the total 9 hydrocephalus cases, 6 developed obstructive and 3 communicating hydrocephalus. The median age of cases with hydrocephalus was 8.6 months. The mean duration of illness prior to admission was 5.7 days and 67% of them have been previously treated with

antibiotics. At admission 89% had altered mental state, 67% had seizures, 44% had neurological deficit. The etiology was proven in 7 cases: *H. influenzae* (4 cases), *N.meningitidis* (2 cases) and *S. pyogenes* (1 case). Case fatality was 22% among cases with hydrocephalus and 4.3% among other cases.

Conclusions: Hydrocephalus as a complication of bacterial meningitis in children was associated with poor outcome and high case fatality. Risk factors for childhood hydrocephalus were infant's age, late admission and infection with *H. influenzae*.

Key words: Bacterial meningitis, hydrocephalus, neurological complications, children

INTRODUCTION

Despite improvements in the diagnosis and treatment of bacterial meningitis in pediatric ages, early and long-term sequelae continue to be of great concern and were reported in many studies (1-9). Risks of long-term disabling sequelae were highest in low-income countries, where the burden of bacterial meningitis is greatest (4). From a systematic review performed on the sequelae of bacterial meningitis in children, the most common severe sequelae were hearing loss (34%), seizures (13%), motor deficits (12%), cognitive defects (9%), hydrocephalus (7%) and visual loss (6%) (9).

Hydrocephalus in one of the severest complications of bacterial meningitis and it can be caused by impaired re-absorption of cerebrospinal fluid (communicating hydrocephalus) or by blockage of cerebrospinal flow (obstructive hydrocephalus). Hydrocephalus is more common complication during neonatal meningitis (10-12), and is rarely reported in bacterial meningitis patients.

OBJECTIVES

The aim of this study was to analyze the incidence, clinical characteristics and risk factors associated with hydrocephalus as a rare complication of childhood bacterial meningitis in a limited resource country during two study periods.

MATERIALS AND METHODS

This study presents a prospective review of children treated for bacterial meningitis in two study periods. In first study period from 1/1/1997 through 12/31/2002, 277 children were prospectively enrolled in the study and in the second study period from 1/1/2009 through 1/1/2010, 77 children were prospectively enrolled in the study. The first study period includes years before and after the war in Kosovo (1999). The second study period includes two years study period, a decade after the war in Kosovo, when the *Haemophilus influenzae type B (Hib)* vaccination in routine childhood immunization programme was also implemented. During the first study period, the diagnose of bacterial meningitis was confirmed by cerebrospinal fluid (CSF) cultures in 124 cases (45%), CSF Gram stain in 111 cases (40%), Hemocultures in 12 cases (4.3%) and latex agglutination test (was done a short period of time) in 15 cases (5.4%) During the second study period the diagnose of bacterial meningitis was confirmed by CSF cultures in 26 cases (34%), CSF Gram stain in 31 cases (40%) and Hemocultures 14 cases (18%). 60 cases (30%) during the first study period and 20 cases (26%) during the second study period were treated for probable bacterial meningitis, based on World Health Organization (WHO) criteria: clinical signs and symptoms of meningitis, changes in CSF, and lack of an identifiable bacterial pathogen. Cases of viral meningitis, tuberculous meningitis and neurobrucellosis were excluded from the study. All CSF samples were forwarded to a reference laboratory for processing, isolation and

identification of pathogens. The facility used was the Department of Microbiology, National Institute of Public Health of Kosovo, which is only in operation 8 am to 2 pm, from Monday to Friday. The low pathogen recovery rate was due in part to previous antibiotic treatment and loss of bacterial viability due to the delayed specimen processing resulting from the laboratory's inadequate hours of operation.

The diagnosis of neurologic complications was made by neurologic examination, neuroimaging, electroencephalography and by neurologist, ophthalmologist, ENT specialist and psychologist evaluation. Indications for performing neuroimaging Computed tomography or Magnetic resonance imaging (CT, MRI) of children following meningitis were: prolonged fever, focal neurological deficit, convulsions, worsening consciousness level, prolonged cyto-biochemical changes in CSF or worsening clinical presentation.

Children are categorized into specific age groups (0-1 years old, >1-6 years of age and >6-16 years of age).

Children treated during the following years at the Infectious diseases Clinic, University Clinical Center of Kosovo, were not included in the study since there was no case of hydrocephalus complicating bacterial meningitis in children beyond the neonatal period.

The research was reviewed and approved by an institutional review board, on 20/04/2018, and a copy of the Approval from Ethical Committee (Number 630) is available for review by the Editor-in-Chief of this journal.

Statistical analysis

Data were analyzed with Stata 9.0. The relative risk and 95% confidence interval was used to quantify the strength of associations of hydrocephalus with children's age groups.

RESULTS

During two study periods (1997-2002 vs. 2009-2010), 277 vs. 77 children (until 16 years of age) were treated for bacterial meningitis at the Infectious Diseases Clinic in Prishtina. Of these cases, 60 (21.7%) vs. 33 (42.8%) children developed neurologic complications, while there were 15 vs.2 deaths, resulting in an overall mortality rate of 5.4% vs. 2.6% (Figure 1).

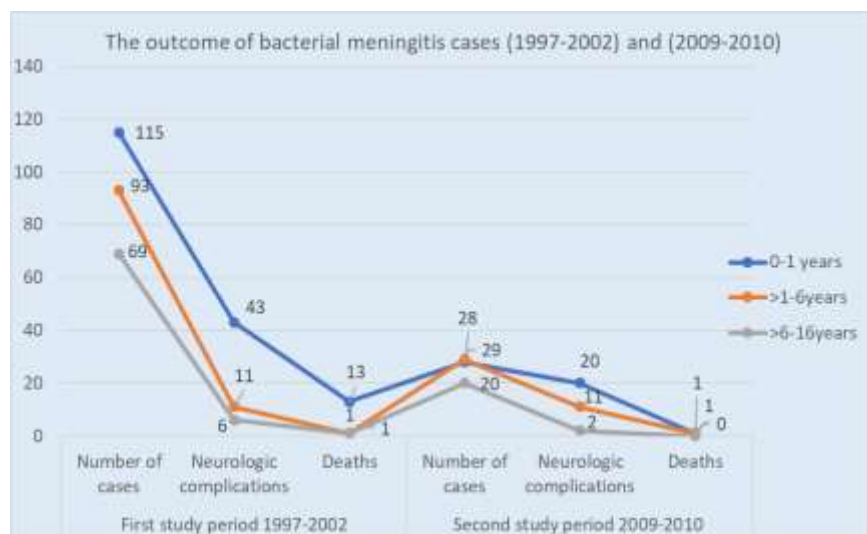


Figure 1 The outcome of bacterial meningitis cases during two study periods: 1997-2002 and 2009-2010

To confirm any suspicion of neurologic complications in bacterial meningitis cases, neuroimaging was performed in 39% (n=109) vs. 58% of children (n=45). Evident structural changes were recorded in 43% (n=47) vs. 75% (n=34) of brain images. Neurologic complications occurred most often in infants in both study periods (43/115 vs. 20/28) and relative risk 3.56

18months). The highest risk for hydrocephalus was observed in infants [Relative risk 2.87; (0.73-11.30)] as in this age group was observed the highest incidence of neurological complications (Table 1).

All children came from rural places, except one. The mean duration of illness prior to admission to our ward of all children with bacterial meningitis

Table 1 Relative Risk for Childhood Hydrocephalus by Age Groups

| Age group | Bacterial meningitis cases (n) | Hydrocephalus cases (n) | % | Relative risk (95% CI) |
|----------------|--------------------------------|-------------------------|-----|------------------------|
| 0 - 1 years | 143 | 6 | 4.2 | 2.87 0.73-11.30 |
| > 1 - 6 years | 122 | 3 | 2.4 | 0.95 0.24-3.74 |
| > 6 - 16 years | 89 | 0 | 0 | 0.16 0.01-2.73 |

n- Number of cases

CI-Confidence interval

(2.17 - 5.92) vs. 2.69 (1.62 - 4.59), was the highest for this age-group.

The most frequent neurologic complications were: subdural effusions (13% vs. 29%), recurrent seizures (11% vs. 8%) and hydrocephalus (2.5% vs. 2.6%).

Hydrocephalus developed equally in both study periods: 2.5% (7/277) vs. 2.6% (2/77). The mean time for confirmation of hydrocephalus was 15.8 days (range 2-38 days). Obstructive hydrocephalus was confirmed in 5/7 vs. 1/2 cases with hydrocephalus.

Of the total cases with hydrocephalus (5 females and 4 males), 6 children were infants and 3 were older than one year. The median age of cases with hydrocephalus was 8.6 months (range 2-

in both study periods was 3.7 vs. 2.2 days while for cases with hydrocephalus was 5.7 days (range 4-7 days).

100/277 (36%) vs. 33/77 (49%) children with bacterial meningitis were previously treated with antibiotics while 6/9 children (67%) with hydrocephalus have been previously treated with antibiotics and admitted to other hospital centers. At admission hydrocephalus cases presented severe clinical forms: 8/9 cases (89%) had altered mental state, 6/9 (67%) manifested seizures, 4/9 (44%) had neurological deficit (Table 2)

Table 2 Clinical Presentation of Bacterial Meningitis Cases

| Clinical presentation at admission | First study period BM cases | Second study period BM cases | Hydrocephalus cases |
|------------------------------------|-----------------------------|------------------------------|---------------------|
| Altered mental state | 141 (51%) | 44 (57%) | 8 (89%) |
| Seizures | 60 (22%) | 14 (18%) | 6 (67%) |
| Neurological deficit | 44 (16%) | 13 (17%) | 4 (44%) |
| Total cases | 277 (100%) | 77 (100%) | 9 (100%) |

BM- bacterial meningitis

At first lumbar puncture of children with hydrocephalus, 7 patients had purulent CSF with > 5000 cells/mm³ and two had pleocytosis > 2000 cells/mm³. At second lumbar puncture performed after 48 hours, 2/9 patients had still purulent CSF. The mean CSF/blood glucose level was 0.23 (range 0.01-0.28) and the mean protein levels in CSF was 2.62 g/L (range 0.75-7.8).

The etiology of bacterial meningitis cases complicated with hydrocephalus was proven in 7 cases: *H. influenzae* 4/25 (16%), *N. meningitidis* 2/103 (2%) and *S. pyogenes* 1/1 case. Childhood hydrocephalus was associated more common with bacterial meningitis due to *H. influenzae*.

Of the total children treated during two study periods (354), 9 children were diagnosed for hydrocephalus (2.5%); 6 were diagnosed for obstructive hydrocephalus and 3 with communicating hydrocephalus. 5 cases underwent external drainage and later placement of permanent ventricular-peritoneal shunt (Figure 2).

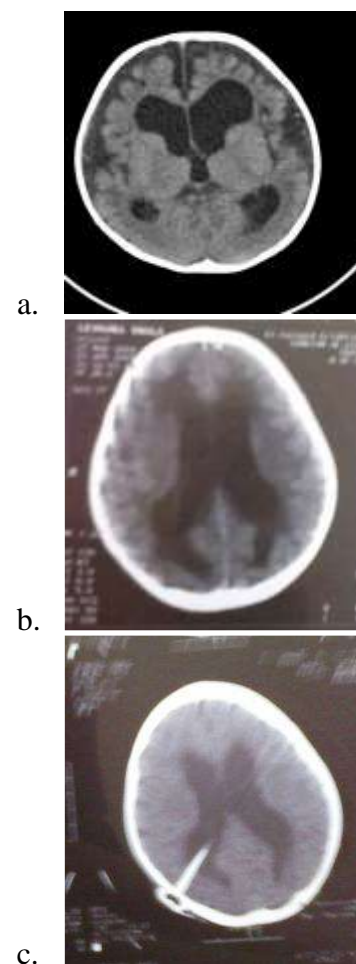


Figure 2 Neuroimages of hydrocephalus cases: a. Hydrocephalus and subdural effusion; b. Obstructive hydrocephalus; c. After shunting

Case fatality was 22% among cases with hydrocephalus and 4.3% among other cases. Of the 9 hydrocephalus cases, two children died and 6/7 cases were left with long-term sequelae: quadriplegia/hemiparesis (2 cases), late seizures (2 cases), neuropsychological impairment (3 cases) and partial amaurosis (1 case). A poorer prognosis and outcome had cases with obstructive hydrocephalus.

DISCUSSION

Despite the improvements in treating childhood bacterial meningitis with appropriate antibiotic therapy, there is still a great percentage of children who experience neurological complications. Chandran A. et al. in their systematic literature search have found that 49% of survivors of childhood bacterial meningitis were reported to have 1 or more long-term sequelae (13). A majority of reported sequelae were behavioral and/or intellectual disorders (45%).

Neurologic complications are common during the acute phase of bacterial meningitis in children with subdural effusion being the most frequent in infants (3). During two study periods (1997-2002 vs. 2009-2010), of the 277 vs. 77 children treated for bacterial meningitis at the Infectious Diseases Clinic in Prishtina, 22% vs. 43% of children developed acute neurologic complications.

According to this study, there was recorded an increased incidence of neurologic complications but decreased mortality rates in the second stage of the study compared to the first stage of the study. There might be several reasons for this,

which include the following: CT scanning was done more frequently during the second study period due to the availability of neuroimaging in our hospital center (82 vs. 54 % of infants); previous antibiotic treatment with inadequate doses before being admitted to our clinic was much higher during the second study period (61 vs. 40 %), and there was no quality and quantity control of antibiotics used during the second study period; the mortality of infants in the second study period was lower compared to the first study period (3.6 vs. 12 %). MRI was not available in our hospital center during the years of our study. During two study periods, almost half of early neurologic complications were resolved within a month by conservative and less often with surgical treatment, while 10 vs. 12 % were left with long-term sequelae predominantly in infants, with most frequent being: late seizures (9 vs. 1 %), deafness (1 vs. 3 %), and neuropsychological impairment (1 vs. 5 %)(3).

Childhood hydrocephalus as a complication of bacterial meningitis beyond the neonatal age is rarely reported in literature. Among patients with hydrocephalus, the age at onset of bacterial meningitis was usually <6 months (14).

In this study, hydrocephalus was found to be the third most common neurological complication after subdural effusions (13% vs. 29%) and recurrent seizures (11% vs. 8%).

The median age of cases with hydrocephalus was 8.6 months and concerning gender almost equally presented. All children came from rural places, except one. Children who developed

hydrocephalus had longer duration of illness prior to admission (the mean duration was 5.7 days) and 67% of them have been previously treated with antibiotics and admitted to others hospital centers. The mean duration of illness prior to admission of children with bacterial meningitis in two study periods was 3.7 vs. 2.2 days (8, 15). The mean time of confirmation of hydrocephalus was 15.8 days (range 2-38 days). Cyto-biochemical changes of CSF were characterized with purulent CSF, low CSF/blood glucose level and increased proteins in CSF, although 67% of them have been previously treated with antibiotics and admitted to others hospital centers. Children with hydrocephalus had the worst outcome compared to children who developed other neurologic complications during the acute phase of bacterial meningitis. At admission hydrocephalus cases presented severe clinical forms: 89% had altered mental state, 67% manifested seizures and 44% had neurological deficit.

Factors associated with increased incidence for developing hydrocephalus during the acute phase of bacterial meningitis in children were: infants age (67%), previous treatment with antibiotics (67%), late admission (the mean duration of illness prior to admission was 5.7 days), presentation of severe clinical form at admission, turbid CSF with high leukocyte content at first lumbar puncture (78%), low CSF/blood glucose level (range 0.01-0.28), high proteins in CSF (range 0.75-7.8), infection with *H. influenzae* 4/25 (16%) and delayed sterilization of CSF (22%) contributing to the blockage of cerebrospinal flow

and re-absorption of CSF. From a recent retrospective study of Huo L, et al. the most significant results of multivariate analysis for hydrocephalus were a rural living situation, altered level of consciousness, previous treatment with antibiotics, initial cerebrospinal fluid protein >2 g/L, C-reactive protein >100 mg/L, and dexamethasone use (14).

The overall rate of hydrocephalus was found equally in both study periods (2.5% vs. 2.6%). From this retrospective study, the incidence of hydrocephalus was found to be much lower compared to the reported rate from many previous studies. Edmond K. et al. in their systematic literature review have found an overall rate of hydrocephalus of 7.1% (4). Bodilsen J. et al. in their retrospective study reported hydrocephalus in 3% of community-acquired bacterial meningitis with case fatality rate of 60% (5). Kasanmoentalib ES. et al. in their prospective cohort study reported a cumulative rate of hydrocephalus of 5% in adult community-acquired bacterial meningitis patients with case fatality rate of 50% (6). Wang KW. et al. in their retrospective single centre study from Taiwan observed a cumulative rate of hydrocephalus of 21% with the overall mortality rate of 50% (7). Hydrocephalus was an independent predictor of death in a multivariate analysis and associated with high fatality rates (6). In this study, the mortality rate of children with hydrocephalus was much lower (22%) compared to the reported rates from previous studies (5-7).

Factors associated with increased case fatality rate (22%) among cases with hydrocephalus were: delayed admission to our specialized ward for treatment of central nervous system infections in children, previous treatment to other hospital centers with inadequate antibiotics missing the main diagnose of bacterial meningitis and severe clinical presentation of hydrocephalus cases.

Of the 9 hydrocephalus cases, two children died and 6/7 cases were left with long-term sequelae.

CONCLUSIONS

In conclusion, hydrocephalus as a complication of bacterial meningitis in children was associated with poor outcome and high case fatality. Risk factors for childhood hydrocephalus were infant's age, late admission and infection with *H. influenzae*.

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Conflict of Interest Disclosure: The authors' have no conflict of interest to declare.

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