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Childhood Acute Bacterial Meningitis: Prognostic Factors for Acute Neurological Complications and Developmental Outcome

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ABSTRACT
Acute bacterial meningitis (ABM) is an inflammatory process of the leptomeninges and the subarachnoid space. It is a serious CNS infection which occurs specially in children <5 years of age and can lead to severe complications. This observational follow up study was carried in the Department of Paediatrics, Institute of Child and Mother Health (ICMH), Matuail, Dhaka, during November 2016 to December 2017, to determine the prognostic factors for acute neurological complications neurodevelopmental outcome in children with acute bacterial meningitis. A total of 56 children with acute bacterial meningitis of age > 1month-15 years admitted in the inpatient department were enrolled in this study. Most 34 (60.7%) of the children belonged to age <12 months and male to female ratio was almost 2:1.More than half (58.9%) children admitted >48hrs after onset of illness, 11(19.6%) children received previous treatment with antibiotics and most (85.7%) of the children had occurrence of seizures prior to admission. Nearly one-third (30%) children were malnourished during admission. Of the 56 studied children 3(5.4%) died and 5(8.9%) children were found to develop various acute complications during discharge. Out of 53 survived, 52(98.1%) children were available for at least one follow-up. Total 11(21.1%) children were found to develop selective neurological complications or impaired developmental outcome in at least one follow up. Regarding acute complications, 3(5.7%) children had hypertonic muscle tone, number of children had exaggerated jerks and squint were same 3(5.7%) during discharge, 2(3.8%) hearing deficit and same number of children had visual deficit during discharge and 1(1.9%) child developed subdural effusion and hemiparesis during hospital stay. Total 11(21.1%) children were found to develop selective neurological complications or impaired developmental outcome in at least one follow up. Hypertonic muscle tone and exaggerated jerk was found in 2(3.8%) children, 5(9.6%) children had developmental regression, 3(5.8%) squint, 2(3.8%) subdural effusion, 2(3.8%) visual deficit, 6(11.5%) hearing deficit and 4(7.7%) had afebrile seizures during follow up. Out of total 5 children who had acute complications, 4 children (80%) developed selected neurological complications or impaired developmental outcome. It was found that, 5(56.25%) children under 12 months of age, 5(62.5%) children who received previous treatment with antibiotics, 4(50.0%) children who had seizures prior to admission, 5 (62.5%) children with high WBC count, 5(71.4%) with hazy CSF colour and 3(37.5%) with CSF glucose/ serum glucose ratio below 0.2 developed acute complications during hospital stay, all of which were statistically significant in bivariate analysis ($p<0.05$). However long term followup is recommended to get more conclusive results.

Keywords: Bacterial Meningitis, Neurological Complications, Developmental Outcome.

I. INTRODUCTION

Acute bacterial meningitis (ABM) is an inflammatory process of the leptomeninges and the subarachnoid space [1]. It is a serious CNS infection which occurs specially in children <5 years of age and can lead to severe complications. Epidemiology of bacterial meningitis has changed greatly in parts of the world with wide spread vaccination in childhood against Haemophilus influenza type b (Hib), Neisseria meningitidis and Streptococcus pneumonia [2]. In addition, antibiotic treatment and good care facilities decreased the occurrence of complications substantially in developed countries but ABM continues to be an important cause of morbidity and mortality in children in developing world[3,4]. Prior to the introduction of antibiotics in the 1940s, case fatality rates for epidemic and endemic bacterial meningitis exceeded 70%. Since then, antibiotic use has reduced case fatality rates significantly[5]. The mortality rate is now

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approximately 5% in industrialized countries and 12-20% in non-industrialized countries, and the longterm morbidity, mainly consisting of persistent neurological sequelae, such as hearing impairment, seizure disorders, and learning and behavioral problems, is 15-20% in the formers and 25-50% in the laters [5,6,7].It has been estimated that 1-2 million cases of acute bacterial meningitis occurs annually across the globe[8]. The global incidence of pneumococcal meningitis in children is 17 cases per 100,000 (O'Brien et al. 2009)[9]. Whereas, the estimated global incidence of Hib meningitis is 31 cases per 100,000 children younger than 5 years [10]. The overall incidence of ABM in developed countries is 2-3/100,000 with peaks of incidence among infants and adolescents [11]. The incidence of ABM among children of developing countries is 10-30/100,000, a figure more than ten times higher compared to Western Europe and the United States [12]. National data regarding ABM is extremely limited in Bangladesh. As of 2000, in south-east Asia, the incidence of pneumococcal meningitis in children is 11-16 cases (average 13) per 100,000 [9], and the incidence of Hib meningitis in children is 11-38 cases (average 27) per 100,000 [10].Developing countries are still facing cases of bacterial meningitis in children due to non-implementation of vaccination programs against meningeal pathogens. The neurological complications resulting from bacterial meningitis include subdural effusions or empyemas, cerebral abscesses, focal neurological deficits (e.g., hearing loss, cranial nerve palsies, hemiparesis, or quadriparesis), hydrocephalus, cerebrovascular abnormalities, altered mental status, and seizures [13,14]. In these studies, complaints >48 hours before admission, coma/impaired consciousness, prolonged duration of seizures, shock, causative pathogen Streptococcus Pneumoniae, young age, male gender, hyponatremia (sodium <130 mEq/L) at admission, mg/dl and CSF/blood glucose ratio below 0.2, high (>1,000) CSF WBC count, CSF protein concentration > 200 and malnutrition were among the prognostic factors found significantly related to adverse outcome [15,16,17]. Proposed the Bacterial Meningitis Score which classifies children at very low risk of bacterial meningitis if they lack all of the following criteria: positive CSF Gram stain, CSF protein level greater than 0.8 g/L, CSF absolute neutrophil count greater than 1000 x 10^6/L, peripheral absolute neutrophil count greater than 10 x 10^9/L, and a history of seizures before or at the time of presentation. But this score is not helpful for assessing prognosis of bacterial meningitis.

II. MATERIALS AND METHODS

Study design: Observational follow up study.

Place of study: Paediatrics Department of ICMH and Child neurology follow up clinic ofPaediatric OPD of ICMH.

Study period: From November 2016 to December 2017

Inclusion criteria: Bacterial meningitis cases were included according to World Health Organization definition [18].

a. Presence of clinical findings such as fever, headache, meningeal irritation findings in accordance with cerebrospinal fluid (CSF) examination showing at least one of the following:

- turbid appearance;
- leukocytosis (>100 cells/mm3);
- leukocytosis (10 - >100 cells/mm3) and either an elevated protein (>100 mg/dL) or decreased glucose (<40 mg/dL)

b. With or withoutLaboratory-confirming by

- growing (culture) or
- identifying (by Gram stain or antigen detection methods) a bacteria pathogen in the CSF or from the blood in a child with clinical syndrome consistent with bacterial meningitis.

2. Age: >01 month to 15 years.

Exclusion criteria:

- Previous neurological deficit, e.g. Cerebral palsy, Epilepsy.
- Neural tube defect such as spina bifida.
- Hydrocephalus with shunt.

Sample size

The sample size was determined using following formula (Daniel)

$n = (Z^2 p\ q)/d^2$, where

So, final sample size, N = n+10% of

n= 53.3+5.3

= 58.6 that is nearer to 59

Study Procedure: All admitted children aged from >1 month to 15 years, satisfying the case definition, was enrolled in the study. Written consent from parents was obtained for each case after explaining the purpose of the study. On admission, the investigator took a detailed history, examined the patient thoroughly and complete the clinical questionnaire. Thereafter, lumbar puncture was performed in each patient except when contraindicated and cerebrospinal fluid (CSF) was sent to the laboratory within hours for cytology and biochemistry. In the microbiology laboratory, CSF was examined by Gram stain and CSF culture was done to detect S pneumoniae, N meningitides and

H influenzae. Blood sample was collected at the same time. Apart from routine investigations in all patients, USG and neuro-imaging of brain was performed according to clinical necessity. Treatment of the cases was started without delay after macroscopic view of CSF, pending the laboratory report. ABM was treated promptly with parenteral antibiotics, steroids and supportive measures. The initial therapy was reviewed on getting the bacteriology report. Patients was monitored twice daily in the morning and evening to evaluate the recovery process or development of complications. Outcome of the disease was noted on the last day during discharge from hospital. During discharge all the children was examined for presence of any acute neurological complication. Questionnaire was filled up. Thorough physical and neurological examination was recorded.

A follow up schedule was maintained. All the enrolled children attended the Child neurology follow up clinic in OPD of ICMH. Total 3 follow ups were taken. 1st follow up was done after 1 month, 2nd and 3rd follow up was done after 3 and 6 months respectively. In each follow up each child was assessed for specific neurological complications and neurodevelopmental outcome. Neurodevelopmental outcome was assessed and recorded using Rapid Neurodevelopmental Assessment (RNDA) tools.

III. DATA ANALYSIS:

Data analysis was done by following procedure:

- Data was checked and cleaned before incorporating into statistical software (SPSS-Version12).
- Categorical data was compared using chi square test and odds ratio and 95% confidence intervals was calculated.
- Multiple regression analysis was done to find out the risk or prognostic factors for development of acute neurological complication and developmental outcome. p-value below 0.05 was considered as significant.

IV. RESULTS

Table I: Distribution of study subjects by socio-demographic characteristics (n=56)

Demographic characteristics	Number of patients	Percentage
Age group		
< 12 months	34	60.7
12 months up to 5 year	16	28.6
More than 5 year	6	10.7
Sex		
Male	38	67.9
Female	18	32.1
Father's occupation		
Farmer	5	8.9
Self employed	18	25
Service	25	44.6
Business	8	14.3
Mother's occupation		
Housewife	54	96.4
Service	1	1.8
Others	1	1.8
Father's education		
No formal education	4	7.1
Primary not completed	7	12.5
Primary completed (up to S.S.C)	16	28.6
S.S.C completed and above	29	51.8
Mother's education		
No formal education	2	3.6
Primary not completed	13	23.2
Primary completed (up to S.S.C)	15	26.8
S.S.C completed and above	26	46.4
Socioeconomic Status		

(Average monthly family income in taka)		
Low income group (Up to 10,000)	9	16.1
Middle income group (10,001 to 20,000)	39	69.6
Upper income group (20,000 +)	8	14.3

Table I shows socio-demographic characteristics of study children, it was observed that 34 (60.7%) children belonged to age <12 month. More than two third (67.9%) children were male. Al-most half (44.6%) of the children's fathers were service holders and maximum (96.4%) children's mothers were housewives. More than half (51.8%) of the children's fathers and almost half (46.4%) of the children's mothers completed S.S.C. About two-third (69.6%) children's average monthly family income was in between TK 10,001 to 20,000.

Table II: Distribution of study subjects by history related to meningitis (n=56)

History	Number of patients	Percentage
Duration of the illness prior to admission		
<48hrs	23	41.1
>48hrs	33	58.9
Previous treatment with antibiotics		
Yes	11	19.6
No	45	80.4
Occurrence of seizures prior to admission		
Yes	48	85.7
No	8	14.3

Table II shows distribution of study subjects by history related to meningitis, it was observed that more than half (58.9%) children admitted >48hrs after onset of illness. 11(19.6%) children took previous treatment with antibiotics. Majority (85.7%) children had occurrence of seizures prior to admission.

Table III: Distribution of study subjects by characteristics of convulsion (n=48)

Characteristics of convulsion	Number of patients	Percentage
Number of episode of convulsion		
1-2	41	85.4
>2	7	14.6
Duration of 1st attack of convulsion		
<15 minutes	41	85.4
>15 minutes	7	14.6
Type of convulsion		
Focal	1	2.1
Generalized	47	97.9

Table III shows characteristics of convulsion among study children and it was observed that 7(14.6%) children had >2 episodes of convulsion before admission. 7(14.6%) children had undergone 1st attack of convulsion lasting for >15 minutes. Only 1(2.1%) child had focal convulsion.

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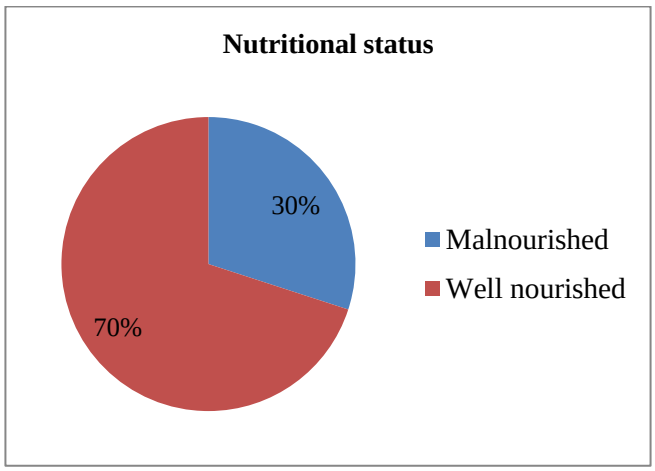

Figure 1: Nutritional status of study subjects.

Figure 1 shows that about one-third (30%) children were malnourished during admission.

Table IV: Distribution of study subjects by signs of meningeal irritation (n=56)

Irritation	Number of patients	Percentage
Neck rigidity	11	19.6
Kernig's sign	6	10.7

Table IV shows presence signs of meningeal irritation among study children during admission and it was observed that 11 (19.6%) children had neck rigidity and 6 (10.7%) children had kernig's sign.

Table V: Distribution of the study subjects by laboratory investigations (n= 56)

Investigation	Number of patients	Percentage
Total WBC count		
Normal	37	66.1
High	19	33.9
Serum Sodium level		
Normal	24	42.9
Low	32	57.1
CSF Colour		
Clear	35	62.5
Hazy	15	26.8
Blood Stained	6	10.7
CSF Cell count (number of cell/cmm)		
Normal (0 to 5)	2	3.6
>5 to 100	32	57.1
>100	22	39.3
CSF glucose /serum glucose ratio		
>0.2	48	85.7
<0.2	8	14.3
CSF protein		
Normal	12	21.4
High	44	78.6

Table V shows status of laboratory investigations of the study children. It was observed that 19(33.9%) children had high WBC count. 32(57.1%) children had low serum sodium level. CSF colour was hazy in case of 15(26.8%) children. More than one third (39.3%) children had

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>100 cell count in their CSF. CSF glucose/ serum glucose ratio was found <0.2 in case of 8(14.3%) children. More than three fourth (78.6%) children had high protein in their CSF.

Table VI: Distribution of the study subjects by Acute complications (n=53)

Acute complications	Number of patients	Percentage
Hypertonic/ increased Muscle Tone	3	5.7
Exaggerated Jerks	3	5.7
Squint	3	5.7
Subdural effusion	1	1.9
Developmental regression	3	5.7
Hemiparesis	1	1.9
Hearing deficit	2	3.8
Visual deficit	2	3.8

Table VI shows presence of acute complications among the study children, it was observed that 3(5.7%) children had hypertonic muscle tone, number of children had exaggerated jerks and squint were same (3, 5.7%) during discharge. 2(3.8%) children had hearing deficit and same number of children had visual deficit during discharge. One (1.9%) child developed subdural effusion and hemiparesis during hospital stay.

Table VII: Distribution of the study subjects by selective neurological complications on follow-up

neurological complication	1st follow up (n=50) n(%)	2nd follow up (n=49) n(%)	3rd follow up (n=43) n(%)
Hypertonic/ increased Muscle Tone	1(2.0)	1(2.0)	1(2.3)
Exaggerated Jerks	1(2.0)	1(2.0)	1(2.3)
Squint	3(6.0)	1(2.0)	1(2.3)
Subdural effusion	2(4.0)	2(4.1)	2(4.7)

Table VII shows presence of selective neurological complications on follow-ups of the study children, it was observed that 1(2.0%, 2.0% and 2.3% on 1st, 2nd and 3rd follow up respectively) child had hypertonic/ increased muscle tone and exaggerated jerks on each follow up. 3(6.0%) children had squint on 1st follow up, 1(2.0% and 2.3%) child had on 2nd and 3rd follow up respectively. 2(4.0%, 4.1% and 4.7% respectively) children had subdural effusion on each follow up.

Table VIII: Overall distribution of children with selected neurological complications and abnormal developmental outcome (found in at least one follow up) (n=52)

Developmental outcome	Number of patients	Percentage
Muscle Tone		
Normal	50	96.2
Hypertonic	2	3.8
Jerks		

Normal	50	96.2
Exaggerated	2	3.8
Squint		
Absent	49	94.2
Present	3	5.8
Subdural effusion		
No	50	96.2
Yes	2	3.8
Developmental regression		
No	47	90.4
Yes	5	9.6
Visual deficit		
Absent	50	96.2
Present	2	3.8
Hearing deficit		
Absent	46	88.5
Present	6	11.5
Seizure		
Absent	48	92.3
Present	4	7.7

Table VIII shows overall distribution of children with selected neurological complications and abnormal developmental outcome. Children found with any selective neurological complication or abnormal developmental outcome in at least one follow up was considered to be abnormal. Hypertonic muscle tone and exaggerated jerk was found in 2(3.8%) children. 5(9.6%) children had developmental regression on follow up. 3 (5.8%) children had squint, 2 (3.8%) children had subdural effusion, 2 (3.8%) children had visual deficit, 6 (11.5%) children had hearing deficit and 4 (7.7%) children had afebrile seizures on follow up.

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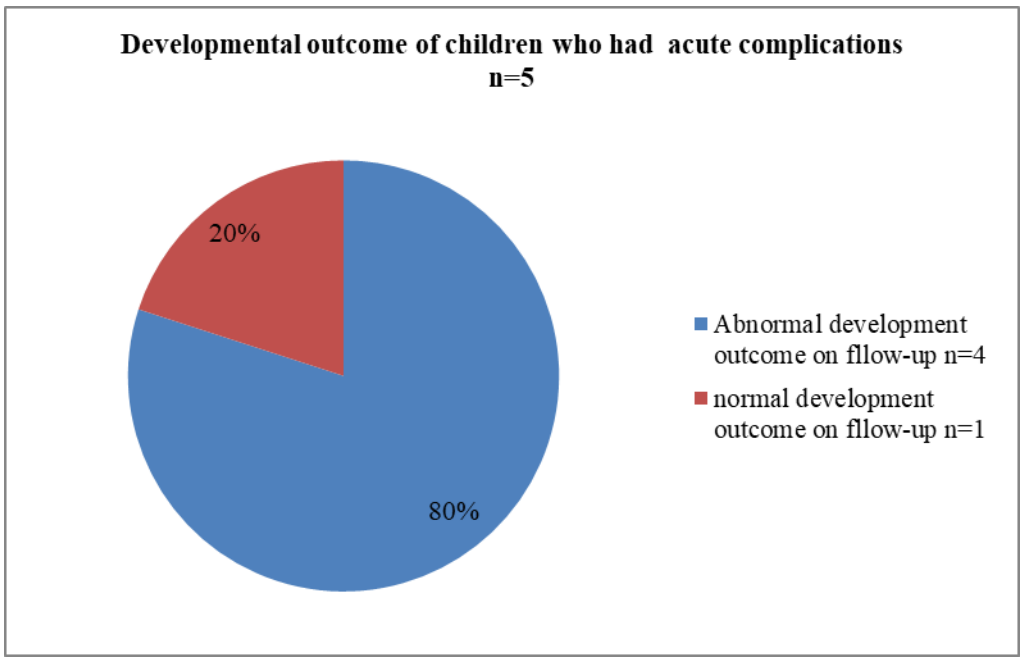

Figure 2: Developmental outcome on follow-up of children who had acute complications.

Figure 2 depicts that 4 (80%) of total 5 children who had acute complications developed abnormal developmental outcome.

Table IX: Association of acute complication with prognostic factors (n=56)

Prognostic factors	Acute complication		p-value
	Present (n=8) n	Absent (n=48) %	
Age group			
< 12 months	5(62.5)	27(56.25)	
>12 months up to 5 year	0(0.0)	18(37.5)	0.011
More than 5 year	3(37.5)	3(6.25)	
Sex			
Male	6(75.0)	32(66.7)	0.640
Female	2(25.0)	16(33.3)	
Duration of the (>48hrs) illness prior to admission			
<48hrs	1(12.5)	22(45.8)	0.076
>48hrs	7(87.5)	26(54.2)	
Previous treatment with antibiotics			
Yes	5(62.5)	7(14.6)	0.012

No	3(37.5)	41(85.4)	
Occurrence of Seizures prior to admission			
Yes	4(50.0)	43(91.5)	0.002
No	4(50.0)	4(8.5)	
Duration of 1st attack of convulsion			
<15 minutes	3(60)	33(75.0)	0.471
>15 minutes	2(40)	11(24.9)	
Type of seizure			
Focal	0(0.0)	1(2.4)	0.755
Generalized	4(100.0)	41(97.6)	
Total WBC count			
Normal	3(37.5)	34(70.8)	0.047
High	5(62.5)	14(29.2)	
Serum sodium level			
Normal	1(16.7)	20(41.7)	0.258
Low	5(83.4)	28(58.3)	
CSF Colour			
Clear	1(14.3)	32(68.1)	0.014
Hazy	5(71.4)	10(21.3)	
Blood Stained	1(14.3)	5(10.6)	
CSF leukocytosis (>100)			
Absent	2(28.6)	32(66.7)	0.446
Present	5(71.5)	16(33.3)	
CSF protein (>200mg/dl)			
Absent	2(25.0)	8(16.8)	0.568
Present	6(75.0)	40(83.7)	
CSF glucose /serum glucose ratio			
>0.2	5(62.5)	43(89.6)	0.042
<0.2	3(37.5)	5(10.4)	

***** Values expressed as numbers (n) and percentages (%) in parenthesis. P value 0.05 was considered as

level of significance. P value was obtained by chi-square test.

Table IX shows association of acute complication with prognostic factors of the study children, it was observed that 5(56.25%) children <12 months of age, 5(62.5%) children with previous treatment with antibiotics, 4(50.0%) children with seizures prior to admission, 5 (62.5%) children with high WBC count, 5(71.4%) children with hazy CSF colour and 3(37.5%) children with CSF glucose/ serum glucose ratio below 0.2 developed acute complication during hospital stay. In all these cases the difference was statistically significant (P<0.05) between two groups.

V. DISCUSSION

The present study findings were discussed and compared with previously published relevant studies. In this study, it was observed that 67.9% children were male and male to female ratio was 2.1:1. Similar findings also observed by George et al [19]. More than half (58.9%) children admitted >48hrs after onset of illness, 11(19.6%) children received previous treatment with antibiotics and most (85.7%) of the children had occurrence of seizures prior to admission. The characteristics of convulsion showed that, 7(14.6%) children had >2 episodes before admission, 7(14.6%) underwent 1st attack of convulsion lasting for >15 minutes and only 1(2.1%) had focal convulsion. In a previous study by Bari et al.,[20] severe acute malnutrition was significantly associated with death and poor outcome. Malnutrition have also been reported as risk factors for poor outcome in a study by Akpede et al [21]. This study found that 30% children were malnourished (moderate acute malnutrition) during admission but it did not show significant association. There was no children with severe acute malnutrition in our study. Out of total 56 study children 3(5.4%) children died during the course of treatment. 5(8.9%) children were found to develop various acute complications during discharge. It was observed that 3 (5.7%) children had hypertonic muscle tone and exaggerated jerks and 3 (5.7%) children developed squint during discharge. 2 (3.8%) children had hearing deficit and same number of children had visual deficit during discharge. One (1.9%) child developed subdural effusion and one other (1.9%) developed hemiparesis during hospital stay. Three (5.7%) children had developmental regression during discharge. Out of 53 survived, 52(98.1%) children were available for at least one follow-up. 50(94.3%) children came during 1st follow up, 49(92.4%) during 2nd follow up, 43(81.1%) during 3rd follow up and 1(1.9%) children did not came for a single follow up. Total 11(21.1%) children were found to develop selective neurological complications or poor developmental outcome in at least one follow up. The study children were examined for the following variables during discharge and follow up: age, gender, duration of the illness prior to admission,< or > 48 hours, previous treatment with antibiotics; occurrence of seizures prior to admission, duration of 1st attack of convulsion occurred prior to admission, type of seizure occurred prior to admission, nutritional status, total leukocyte count, serum sodium level, CSF Colour, CSF cytology, CSF protein and CSF glucose /serum glucose ratio. Children under 12 months of age, children who received previous treatment with antibiotics, children having occurrence of seizures prior to admission, with high WBC count, with hazy CSF colour and with CSF glucose/ serum glucose ratio below 0.2 were significantly (p<0.05) associated with acute complications during hospital stay. Children with focal seizure and children with hazy CSF colour were significantly (p<0.05) associated to have impaired developmental outcome.Young age (indicated as younger than two years old), is considered an important prognostic factor for adverse outcome of children with bacterial meningitis [22,23]. In Namani et al [24] study, age < 12 months was also identified as predictor for neurological complications. In a study by Bari et al., [20] it was found that mortality under one year was maximum. Our study found that 56.25% of children aged below 12 months developed acute complication during hospital stay which was statistically significant (P<0.05) and the result is similar to previous studies. In this study it was found that 62.5% children with previous treatment with antibiotics significantly (P<0.05) developed acute complication. Pre-hospital antibiotic treatment was found to be associated with adverse outcome (death or neurological sequelae) in children with meningitis in a study conducted by Akpede et al.,[21] which supports our study, though Kaaresen et al [25] did not find any association between pre-hospital oral or parenteral antibiotic therapy and outcome. Severity of clinical presentation, manifested by the occurrence of seizures, are identified as one of the strongest prognostic factors for neurological complications in the current study, similar to that indicated in numerous studies from developed [26,17] and developing countries [28,29]. In our study, 50.0% children with seizures prior to admission developed acute complication during hospital stay which was statistically significant (p<0.05).

VI. LIMITATIONS

- The study population was selected from one selected hospital in Dhaka city, so that the results of the study may not be reflect the exact picture of the country.
- The present study was conducted at a very short period of time and only 6 month follow up was done.
- CSF culture could not be performed in many cases due to resource constraint. So organism specific complications could not be identified here.
- Small sample size was also a limitation of this study.

VII. CONCLUSION

This study was undertaken to analyze the prognostic factors for acute neurological complications and neurodevelopmental outcome of childhood acute bacterial meningitis. Majority of the children were age less than 12 months and male were predominant. Out of total 56 study children 3(5.4%) children died during the course of treatment and 5(8.9%) children developed various acute complications during discharge. Four (80.0%) out of 5 children having acute complications developed abnormal developmental outcome. Children under 12 months of age, children who received previous treatment with antibiotics, seizures prior to admission, high WBC count, hazy CSF colour and CSF glucose/ serum glucose ratio below 0.2 were significantly ($p<0.05$) associated with acute complications during hospital stay. Children with focal seizure and children with hazy CSF colour were significantly ($p<0.05$) associated to abnormal developmental outcome. Acute complications not significantly ($p>0.05$) associated with prognostic factors in multivariate regression analysis but age under 12 months, CSF leukocytosis and CSF glucose/serum glucose raito<0.2 were significantly associated with abnormal developmental outcome in multivariate regression analysis.

Recommendations

A multi centered study with large sample is recommended. However long term follow up is necessary to get a conclusive results.

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