

# Outcome and prognostic factors of acute meningoencephalitis in children of Southern Bangladesh

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## Abstract

**Objective:** To estimate the outcome of acute meningoencephalitis (AME) in children and evaluate the impact of prognostic factors.

**Design and setting:** A prospective cross sectional study was conducted in the paediatric ward of Khulna Medical College Hospital from 2007- 2009.

**Method:** All admitted children, aged 1 month to 12 years, satisfying the case definition were enrolled into the study. Cerebrospinal fluid (CSF) was collected for cytology and biochemistry to categorize AME into pyogenic, viral or normal varieties. CSF was tested for common bacterial antigen and, along with serum was also tested for Japanese encephalitis virus antibodies. Patients were monitored twice daily until the final outcome.

**Results:** One hundred and forty children were inducted constituting 2.5% of admissions. Infants (30%) were the worst sufferers. Twenty one (15%) children with AME died which is 4 times higher than the overall mortality (3.8%) in paediatric ward ( $p < 0.001$ ). Among the 11 bacteria positive cases one died from *S Pneumoniae*. Low GCS score was associated with higher mortality ( $p < 0.05$ ). Eighteen (13%) cases developed neurological sequelae. Paralysis (27%) was the most frequent followed by hydrocephalus (23%) and involuntary movements (14%). Number of sequelae was significantly higher in pyogenic (44%) meningoencephalitis in comparison to non-pyogenic (14%) variants (OR=3.30, 95% CI: 1.08-10.01,  $p < 0.05$ ).

**Conclusions:** Mortality from AME was 15%. Low GCS score was associated with higher fatality.

(Key Words: Outcome; prognostic factors; meningoencephalitis; Bangladesh)

## Introduction

Acute meningoencephalitis (AME) designates an inflammatory process involving both the meninges and brain parenchyma<sup>1,2</sup>. The organism that causes meningitis often also causes encephalitis and the reverse is true as well<sup>3</sup>. The onset of the disease is usually abrupt, diagnostically confusing and may lead to death or disability if appropriate therapy is not instituted quickly<sup>4</sup>. AME remains a neurological and infectious disease emergency with a high mortality rate, despite advances in diagnostic technique, antimicrobial therapy and adjuvant use of anti-inflammatory agents<sup>2,4</sup>.

The incidence of acute bacterial meningitis (ABM) in the developed countries is 2-3/100,000 with peaks of incidence in infants and adolescents<sup>5</sup>. Its incidence among children of developing countries is 10-20/100,000, more than ten times higher than in Western Europe and the United States<sup>6</sup>. Mortality rate and lifelong sequelae including deafness, epilepsy and mental retardation, can reach 12-50% in resource poor countries and young children are the group at highest risk<sup>6</sup>.

The overall incidence of viral meningoencephalitis (VME) was found to be 10.5/100,000 in children with the highest figure (18.4%) in infants<sup>7</sup>. An unexpected outbreak of VME has occurred in Asia by enterovirus and Nipah virus in the recent past<sup>1</sup>. Japanese encephalitis (JE), a mosquito borne viral disease is highly endemic in Southern India<sup>8,9</sup>. It has high (30%) case fatality and about 50% of survivors bear the neurological sequelae<sup>9</sup>. The commonest cause of viral encephalitis in UK is herpes simplex type1<sup>1</sup>. Poor prognostic factors for herpes encephalitis include reduced Glasgow Coma Scale (GCS) score and delay in starting supportive therapy. Two thirds of survivors have significant neuropsychiatric sequelae including memory impairment<sup>10</sup>. Nipah outbreaks occurred eight times in northwestern Bangladesh in the last decade with high case fatality (43-63%)<sup>11,12</sup>. National data regarding the outcome of AME is extremely

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limited in Bangladesh. Therefore this study was undertaken to estimate the outcome of AME and to evaluate the prognostic factors related to it.

## Method

A prospective study was conducted in the paediatric ward of Khulna Medical College Hospital (KMCH), a referral hospital for all the districts of Khulna division in Southern Bangladesh. KMCH is a 500 bed hospital with 50 paediatric beds. The study continued for two years from October 2007 to September 2009. All admitted children aged between 1 month and 12 years, satisfying the case definition, were enrolled in study. AME was defined as acute onset of fever (1-14 days) followed by any one of the following (a) signs of meningeal irritation (b) convulsion or (c) change in mental status<sup>13</sup>. Children diagnosed later as febrile convulsion, cerebral palsy, stroke and epilepsy were excluded from the study. Written consent from parents was obtained for each case after explaining the purpose of the study. Ethical clearance was obtained from the ethical review committee of KMCH.

On admission, a trained medical officer took a detailed history, examined the patient thoroughly and completed 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 latex agglutination test (LAT) to detect *S pneumoniae*, *N meningitides* and *H influenzae*. Blood sample was collected at the same time. Separated serum and the remaining CSF were kept in a deep freezer and transported to the virology laboratory (Institute of Public Health) in a cool box at two week intervals for detection of JE virus immunoglobulin M (IgM) antibodies by capture enzyme-linked immunosorbent assays. Apart from routine investigations in all patients,

brain imaging 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<sup>14</sup>. Other cases were treated symptomatically and by supportive therapy. CSF findings were categorized as viral or pyogenic on the following criteria<sup>1,15</sup>: (a) Viral: pressure-normal to high, colour-clear, cell/cu mm<1000, differentials-lymphocyte, CSF: plasma glucose ratio >0.3 and protein 0.5-1g/L (b) Pyogenic: pressure high, colour cloudy, cell/cu mm >1000, differential neutrophil, CSF: plasma glucose ratio <0.3 and protein >1g/L. Patients were 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.

The questionnaires, at the end of the study, were checked and cleaned before incorporating into statistical software (SPSS-Version12). Categorical data were compared using chi square test and odds ratio and 95% confidence intervals were calculated. Continuous data was compared by independent sample t test. In all tests two tailed p value were used and value below 0.05 was considered as significant.

## Results

A total of 5605 children (1month-12 years) got admitted to hospital during the study period of two years and 213 (3.8%) of them died. During the same period 140 children of AME were enrolled in the study among which 21 (15%) died. Demography of the studied children is shown in Table-I.

**Table 1: Demography of studied children**

	Group	Number	Percentage
<b>Age</b>	1-48 months	64	45.7
	49-96 months	43	30.7
	97-144 months	33	23.6
<b>Sex</b>	Male	82	58.6
	Female	58	41.4
<b>Religion</b>	Muslim	132	94.3
	Hindu	8	5.7
<b>Home District</b>	Khulna	80	57.1
	Jessore	45	32.1
	Kushtia	7	5.1
	Others	8	5.7

Sixty four (46%) children belonged to the age group 1 to 48 months and 41 (29%) of them were infants. Mean (SD) age of the patients was 60(46) months with the age range from 1 to 144 months. Male children suffered more than the female with a ratio of 1.4:1. Regional distribution of cases was done on the basis of older district and 80 (57%)

children belonged to Khulna district followed by 45 (32%) children from Jessore district.

According to CSF report, patients were divided into 3 categories (Table 2).

**Table 2: Outcome of AME in relation to CSF biochemistry**

CSF	Improved	Partially improved	Expired	Unknown	Total (%)
Normal	59	10	15	9	93 (66.4)
Pyogenic	14	6	3	1	24 (17.1)
Viral	10	1	1	1	13 (9.3)
LP-Not Done	7	1	2	0	10 (7.1)
Total (%)	90 (64.3)	18 (12.9)	21 (15.0)	11 (7.9)	140 (100)

Besides 21 fatalities, 90 (64%) cases improved completely and 18 (13%) children developed complications. In 24 (17%) cases CSF was found to be pyogenic and in 13 (9%) children it was compatible with VME. Case fatality rate was compared between pyogenic (14%) and non-pyogenic (18%) variants and no significant relationship was found between them (OR=0.78; 95% CI: 0.17-3.17; p=0.495). Among the 11 cases

of bacterial detection, 8 were *S pneumoniae*, 2 were *H influenzae* and 1 was *N meningitides*. Out of 8 *S pneumoniae* cases 1 died and two developed paralysis. JE virus was detected in 3 cases and 1 of them developed involuntary movements.

Impact of different prognostic factors was compared between the dead and survivors (Table 3).

**Table 3: Impact of prognostic factors between the dead and survivors**

Risk factors	Group	Dead (%)	Survivors (%)	p value
<b>Age</b>	1- 48 months	8 (5.7)	56 (40)	0.686
	49-96 months	8 (5.7)	35 (25)	
	97- 144 months	5 (3.6)	28 (20)	
<b>Sex</b>	Male	13 (9.3)	69 (49.3)	0.923
	Female	8 (5.7)	50 (35.7)	
<b>Seizure</b>	Yes	19 (13.6)	98 (70)	0.527
	No	2 (1.4)	21 (15)	
<b>Mental status</b>	Coma	12 (8.6)	45 (32.1)	0.115
	Confusion	9 (6.4)	60 (42.9)	
	Normal	0 (0)	14 (10.0)	
<b>Prodromal phase</b>	Mean (SD) days	4.9 (3.5)	4.2 (3.3)	0.405
<b>GCS score</b>	(Mean (SD)	6.1 (2.3)	7.3 (3.2)	0.049
<b>Hospital stay</b>	Mean (SD)days	2.6 (1.8)	9.6 (5.5)	<0.001

No significant association of mortality was found with age and sex. Proportion of seizure and coma were higher in fatal cases but was not statistically significant. However low GCS score (p<0.05) at admission was significantly related to higher fatality. Prodromal phase as calculated from onset of fever to neurological feature ranged from 1 to 14 days and the overall mean (SD) period was 4.3

(3.4) days. No correlation was found between prodromal phase and outcome of the disease.

Neurological sequelae were found in 18 (13%) partially improved cases and four patients had more than one sequelae (Table 4).

**Table 4: Sequelae of AME in relation to CSF findings**

Sequelae	Normal (93)	Pyogenic (24)	Viral (13)	LP-Not Done (10)	Total (%)
Paralysis	3	2	0	1	6 (27.3)
Hydrocephalus	3	2	0	0	5 (22.7)
Involuntary Movement	1	1	1	0	3 (13.6)
Epilepsy	1	1	0	0	2 (9.1)
Cerebral abscess	1	1	0	0	2 (9.1)
Blindness	1	1	0	0	2 (9.1)
Deafness	0	0	1	0	1 (4.6)
Emotional disorder	1	0	0	0	1 (4.6)
<b>Total</b>	10+1*	6+2*	1+1*	1	18+4*

\* Four patients had two or more sequelae

Paresis/Paralysis was highest (6) in frequency followed by hydrocephalus (5) and involuntary movement (3). Number of sequelae from pyogenic meningoencephalitis (44%) was compared with that of nonpyogenic variants (14%) and the difference was found to be statistically significant (OR= 3.30, 95% CI: 1.08-10.01, p<0.05).

### Discussion

The study cases constituted 2.5% of total cases in paediatric ward of KMCH. Young children were primarily affected and infants (29%) were the worst sufferers. No differences of affected children were found in respect to sex, religion and geographical location. AME is a significant cause of morbidity in children across all age groups; however mortality and neurological sequelae are particularly high in young children<sup>16-18</sup>. In India, among all the paediatric admissions, 1.5% cases were due to bacterial meningitis with a mean case fatality of 16%<sup>19</sup>. Kabilan noticed that 70% of JE cases were in the 3-8 year age group and both sexes were equally affected<sup>13</sup>.

Twenty one children (15%) with AME expired during this study. This was 4 times higher than the overall mortality (3.8%). However 64% recovered completely from the illness. Mortality between pyogenic (14%) and non-pyogenic AME (18%) was not significantly different. Single fatality was noticed with bacterial meningitis due to *S pneumoniae*. The case fatality (24%) for all types of meningoencephalitis in Egypt is higher than what is reported from United States and Europe possibly due to high level of antimicrobial resistance<sup>20</sup>. In another study, mean case fatality was 16% and fatality in bacterial meningitis was 36% compared to 14% in bacterial negative group<sup>14,19</sup>. On the other hand, case fatality from JE was high (20-30%) and much higher (83%) from

Nipah encephalitis<sup>21,22</sup>. This study supports those findings with ABM, considering pneumococcus as a virulent organism. However, the outcome of a small number of JE cases is beyond the scope of a valid comment.

Prognosis of AME may be anticipated by some clinical factors. Seven prognostic factors were compared between the dead and survivors. Although the proportion of cases was quite different between the two groups, statistical significance could not be established with age, sex, seizure, mental status and prodromal phase. However Low GCS score (p=0.049) was significantly associated with higher mortality. Recovery from VME depends upon severity of illness, specific cause and age of the child<sup>3</sup>. Ramakrishnan observed that reduced level of consciousness doubled the mortality and sequelae in comparison to normal consciousness<sup>5</sup>. In India, the mean GCS score among 42 JE patients was 6 and eight of them died between 2 weeks to 2 months<sup>23</sup>.

Eighteen (13%) cases developed 22 sequelae. Paralysis (27%) was highest in frequency followed by hydrocephalus (23%) and involuntary movement (14%). Two cases with *S pneumoniae* and one case with JE virus developed sequelae. During AME, many children suffer acute complications such as seizures, high intracranial pressure and coma, but some of them develop long term neurological deficit<sup>3</sup>. In Mexico the common neurological sequelae from acute bacterial meningitis were seizure disorders (37%) and hearing loss (32%)<sup>24</sup>. In cases with severe parenchymal involvement, 30-40% children develop potential deficits in intellectual, motor, psychiatric, visual and auditory functions<sup>25,26</sup>. The picture with viral meningoencephalitis is quite different as reported by WHO, where about 30%

patients admitted with JE died and 50% survivors had neurological sequelae<sup>8</sup>. Mcgrath noticed significant neuropsychiatric sequelae in two thirds of herpes encephalitis survivors<sup>10</sup>. The sequelae in this series were much less possibly because of missing sequelae with late appearance. Prehospital antibiotic use and early corticosteroid therapy in hospital might also have had some beneficial role.

Primary limitation of this study was failure to follow up the cases for a minimum of three months which could have better delineated the permanent neurological deficits. Some patient in the study group left the hospital on their own desire depriving full observation. Furthermore, a large number of biochemically normal and viral CSF remained unexplored to other virus limiting establishment of causal relationship with outcome.

### Conclusions

- AME is associated with a high mortality.
- Low GCS score is significantly associated with a high fatality.
- Motor deficit and hydrocephalus are the dominant sequelae from AME.
- Urgent hospitalization and immediate treatment are crucial for better outcome.

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