Research Paper

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Acute Febrile Encephalopathy in Children and Predictors of Mortality.

Medical Science

KEYWORDS : Acute febrile encephalopathy (AFE), Children, Mortality, Predictors.

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ABSTRACT

Background: Incidence of acute febrile encephalopathy (AFE) is high in children and associated with high mortality and sequela. Limited data is available about predictors of mortality in children of AFE from central India.

Aim: To study the predictors of mortality in children of AFE.

Methods: This is observational, prospective study, carried out in a tertiary care hospital of central India. Duration of the study was two years (2010 to 2012). One hundred and seventy six children in the age group of one month to 12 years, presented with fever ≤ 2wks duration and altered mental status lasting for more than 4h were enrolled in the study. Outcome was evaluated in the study subjects. Data was analysed by use of Chi-square test, Fisher's exact test and multivariate regression. P-value ≤ 0.05 was considered statistically significant.

Results: Maximum enrolled children were of viral encephalitis (46.59%) and rest, were of pyogenic meningitis, tuberculosis meningitis and cerebral malaria. Among independently significant variables, shock, severe anaemia, bradycardia, Glasgow coma scale (GCS) of less than eight and refractory seizures were found to be significant and other variables like respiratory failure, multiorgan dysfunction syndrome and abnormal coagulation profile were found insignificant on full model of multivariate regression analysis.

Conclusion: Refractory seizures, GCS <8, bradycardia, shock and severe anaemia were independent predictors for mortality in children of AFE.

Introduction:

"Acute febrile encephalopathy" (AFE) is a term commonly used to identify the condition in which altered mental status either accompanies or follows short febrile illness [1,2]. Non-traumatic coma is a common condition in children leading to hospital admissions [3]. The profile of AFE varies across different geographic regions and in different seasons in the same area. Despite much epidemiological investigation, the presentation with acute onset fever and altered sensorium has often remained mystery, especially in Indian states of Uttarpradesh, Bihar and West Bangal [3–5].

Majority of the studies revealed etiology of AFE, but very few studies emphasized on predictors of mortality. Indian study found that clinical signs were good predictors of outcome [4]. In view of large burden of AFE in pediatric age group and high mortality associated with it, there is paucity of studies from central India regarding factors predicting mortality in these patients. Hence, this study is planned to study the predictors of mortality in children of AFE.

Methods

The present observational, prospective study was conducted at a tertiary care hospital of central India from October 2010 to October 2012. Ethical clearance was sought for from institutional ethical committee before start of the study.

Children of either sex, aged between one month to 12 year presented with fever (rectal temperature < 38oC) and alteration of consciousness lasting for more than 4h were enrolled in study. However, children with metabolic encephalopathy, intracranial space occupying lesion, febrile seizure, endocrinal encephalopathy and stroke were excluded.

Sample size [5] was calculated by estimating difference between two proportions of death in patient with GCS<8 and proportion of death in patient with GCS ≥ 8. Considering confidence interval of < 95%, sample size estimated was 176.

All enrolled subjects were evaluated for presence of factors predicting mortality like GCS (at the time of admission), shock, severe anaemia, multiorgan dysfunction syndrome (MODS), refractory seizures, renal failure, respiratory failure, liver failure, abnormal coagulation profile (abnormal prothrombin time and/or activated partial thromboplastin time) and clinical features of raised intracranial tension. Enrolled subjects were investigated and managed with specific treatment. They were also evaluated for outcome and follow up is done on 30th day for presence of sequela.

StatisticalAnalysis

Conducted using STATA version 10.0. Descriptive statistics were expressed as mean and standard deviation. Data was analyzed by use of Chi-square test and Fisher's exact test was performed to test for differences in proportions of categorical variables between two or more groups. The level of $p<0.05$ is considered significant. Multivariate regression analysis was done in this study.

Results

Out of 176 enrolled subjects, maximum subjects (60, 34.09%) belonged to the age group of 3-6 y however, mean age was 5.77±3.22 y. Proportion of male and females were 59.66% and 40.34% respectively. Etiological distribution of subjects showed maximum (82, 46.59%) were of viral encephalitis; others were pyogenic meningitis (39, 22.16%), cerebral malaria (28, 15.90%) and tuberculosis meningitis (27, 15.35%).

[Table/Fig-1] Showed that out of 176 subjects, 34 (19.31%) subjects were died and 47 (26.71%) developed sequelae. Maximum mortality (15, 44.11%) was due to viral encephalitis, while least (5, 14.70%) was due to pyogenic meningitis.

(table one comes here)

Also, maximum mortality (15, 40.55%) was seen in age group of one month to 3y and least mortality seen in the age group of 3-6 y. Mortality was more in females (16, 22.53%) than in males. Sequela was maximum (17, 36.17%) in tuberculosis meningitis and minimum (3, 6.38%) in cerebral malaria.

[Table/Fig-2] revealed that out of 94 subjects who had GCS <8 at the time of admission, 27 (28.72%) were died. Subjects with GCS <8 had 4.32 times higher risk of death (Odd's ratio- 4.32,CI=1.68-12.43) as compared to subjects who had GCS ≥8. This was found to be statistically significant (p = 0.001). Similarly presence of variables like refractory seizures, bradycardia, shock, severe anaemia, MODS, abnormal coagulation profile and respiratory failure had significant risk of death. Presence of variables like liver failure, renal failure and clinical features of raised intracranial tension was associated with higher risk of death and it was not statistically significant. For these variables, Odd's ratio was in the range of 1.21 to 3.43.

(table 2 comes here)

[Table/Fig-3] showed that out of eight independently significant variables, only five variables i.e. refractory seizures, GCS <8, bradycardia, shock and severe anaemia were found to be significant on full model of multivariate regression analysis. Other variables like MODS, abnormal coagulation profile and respiratory failure were not found significant on full model of multivariate regression analysis.

(table 3 comes here)

Discussion

Physicians are often faced with the task of predicting the outcome of patients in coma as it is important to efficiently and optimally utilize resources. This point out the need for development of simple and applicable variables and these can be used as predictors of mortality in AFE.

In our study, out of 176 children, 59.65% were males and 40.34% were females. Maximum subjects were from the age group of 3-6 y (34.09%), this finding is consistent with recent published studies [4,6]. Out of 176 subjects, 46.59% were diagnosed as viral encephalitis, 22.15% as pyogenic meningitis, 15.34% as tuberculosis meningitis and 15.90% as cerebral malaria. Bansal A et al., [4] studied non-traumatic coma in 100 subjects and found viral encephalitis in 30%, tuberculosis meningitis in 31.66%, pyogenic meningitis in 26.66%, and cerebral malaria in 3.33%. A recent study from India [7] found viral encephalitis in 12%, tuberculosis meningitis in 8%, pyogenic meningitis in 6% and cerebral malaria in 1%. This difference can be attributed to sampling and this can be inferred that the infective pathology is most common cause of AFE in India.

We found mortality of 19.31% and 26.70% subjects had sequela. A study from India [2] enrolled 127 patients with fever and altered sensorium, reported mortality of 16.5% and mortality was more in subjects of acute encephalitis. A study from Iran [8] also reported mortality of 16.6% and sequela of 28.66%. However, a study from Nigeria [9] reported higher mortality of 32.5%. This difference in mortality can be explained by the difference in aetiology, and diagnostic and treatment facilities. Similar to a study from Iran [8] and Wong CP et al., [10], we found higher mortality in age group of one month to 3y (15, 40.55%). In our study, we found higher mortality in females (16, 22.55%) and it was similar to previous studies [4,11]. However, Khodapanahandeh F et al., [8] and Wong CP et al., [10] found no sex difference in mortality.

We found maximum mortality in viral encephalitis and least in pyogenic meningitis. Maximum sequela was found in tuberculosis meningitis and least in cerebral malaria. This could be due to availability of early diagnostic and prompt treatment facility at this level. This observation was similar to Bansal A et al., [4], who found maximum sequela in tuberculosis meningitis and no sequela in cerebral malaria. However, Idro R et al.,[11] found high sequela (23.8%) in patients of cerebral malaria.

In present study, GCS <8 had 4.32 times higher risk of death (Odds ratio: 4.32) and was found to be statistically significant (p=0.001). This result was in accordance with the previous studies [4,12]. NayanPrabha PC et al.,[13] also reported high mortality in patients of GCS < 8 and also found that ocular and motor score is more important than overall GCS score. However, a study from Saudi Arabia reported no relation between GCS and mortality [14]. Similar to previously published study [4], bradycardia was associated with high mortality and it was statistically significant. However, Buch PM et al., [6] and Ahmed S et al., [12] found no statistically significant association of bradycardia with mortality. So, bradycardia as a predictor of mortality needs further evaluation. Presence of refractory seizures was significantly associated with mortality and it is consistent with study of Sahin M et al., [15] who studied outcome of severe refractory seizures in 22 children aged 4.5 months to 18y and found mortality of 39%. Subjects who had hypotension at the time of admission had 2.46 times more risk of death than those subjects without hypotension. This was in accordance with published studies [4,6,11]. Similar to Buch PM et al., [6], severe anaemia significantly associated with mortality.

Presence of variables in AFE like MODS, abnormal coagulation profile and respiratory failure has higher risk of death and it was statistically significant. Buch et al., [6] also studied variables associated with AFE and found that severe malnutrition, severe anaemia, severe dehydration and jaundice correlated significantly with mortality. Although, physicians usually attempt to take a wide range of factors into account when making clinical decisions and assessing prognosis, there is less probability in this effort to be complete.

Ideal study is a community based multicentre study. To identify neurological and functional deficits among survivors, long follow up is required. Aetiological agent could not be identified in viral encephalitis.

Conclusion

Mortality was higher in subjects of viral encephalitis and in the younger age group (one month to 3y). Sequela was higher in the subjects of tuberculosis meningitis and in the age group of 6-9 y. Refractory seizures, GCS <8, bradycardia, shock and severe anaemia were independent predictors for mortality in children of AFE.

Table 1: Distribution of AFE and outcome as per aetiology

Outcome	Etiology				
	Viral encephalitis	Pyogenic meningitis	Tubercular meningitis	Cerebral malaria	Total
Survival	52(54.74%)	22(23.16%)	2(2.10%)	19(20.0%)	95 (53.98%)
Sequela	15(31.92%)	12(25.53%)	17(36.17%)	3(6.38%)	47 (26.71%)
Death	15(44.11%)	5(14.70%)	8(23.52%)	6(17.64%)	34 (19.31%)
Total	82	39	27	28	176

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Table 2: Outcome of AFE and predictor variables

Variables	Present/ Absent	No (%)	Death (%)	Survival (%)	Confi-dence interval	Odd's ratio	p-value
GCS	<8	94(53.40)	27(28.72)	67(71.28)	1.68-12.43	4.32	0.001
	≥8	82(46.60)	7(8.53)	75(91.47)			
Refr-actory seizure	Present	62(35.22)	20(32.26)	42(67.74)	1.46-7.97	3.4	0.001
	Absent	114(64.78)	14(12.28)	100(87.72)			
Brady-cardia	Present	49(27.84)	17(34.69)	32(65.31)	1.45-8.03	3.43	0.001
	Absent	127(72.16)	17(13.38)	110(86.62)			
Shock	Present	94(53.40)	24(25.53)	70(74.46)	1.04-6.19	2.46	0.025
	Absent	82(46.60)	10(12.19)	72(87.80)			
Respi-ratory failure	Present	52(29.54)	17(32.69)	35(67.31)	1.30-7.10	3.05	0.003
	Absent	124(70.46)	17(13.70)	107(86.30)			
Severe ana-emia	Present	93(52.84)	24(25.80)	69(74.19)	1.07-6.37	2.54	0.021
	Absent	83(47.16)	10(12.04)	23(87.96)			
MODS	Present	69(39.20)	19(27.53)	50(72.47)	1.01-5.37	2.33	0.026
	Absent	107(60.80)	15(14.01)	92(85.99)			
Abn-ormalcoag-ulation profile	Present	74(42.04)	20(27.07)	54(72.97)	1.01-540	2.32	0.027
	Absent	102(57.96)	14(13.72)	88(86.28)			
Incre-ased ICT	Present	100(56.81)	24(24.00)	76(76.00)	0.88-5.23	2.08	0.071
	Absent	76(43.19)	10(13.15)	66(86.85)			
Liver failure	Present	54(30.68)	13(24.07)	41(75.93)	0.63-3.54	1.52	0.288
	Absent	122(69.32)	21(17.21)	101(82.79)			
Renal failure	Present	61(34.65)	13(21.31)	48(78.68)	0.51-2.79	1.21	0.626
	Absent	115(65.35)	21(18.26)	94(81.74)			
GCS- Glasgow coma score, MODS- multiorgan dysfunction syndrome, ICT- intracranial tension							

Table 3: Full model of multivariate regression analysis of significant variables in AFE.

Outcome	Adjusted Odd's ratio	Adjusted P value	Adjusted 95% CI
MODS	0.7467	0.654	0.2084-2.6744
Refractory seizures	3.057	0.017	1.2204-7.6661
GCS<8	2.835	0.035	1.0747-7.4840
Bradycardia	5.280	0.006	1.6225-7.1870
Shock	6.202	0.001	2.0289-8.9617
Respiratory failure	1.958	0.281	0.5770-6.6468
Severe anaemia	4.338	0.004	1.6036-11.7355
Bleeding diathesis	0.901	0.864	0.2732-2.9714

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