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Original Article

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Abstract

Objective: To determine the common etiological features of non-traumatic coma in children and evaluate possible predictors of morbidity and mortality in these patients.

Method: A cross sectional study was carried out at the Paediatric Department of Civil Hospital Karachi from February 2008 to February 2009. In total 100 children, up to 14 years of age having history of non-traumatic coma were included. At the time of enrolment demographic data, clinical features, laboratory parameters and radiological workup were recorded. Data was entered and analyzed with SPSS version 16. Descriptive statistics were generated for all variables. Relationships between categorical variables were evaluated by examining cross-tabulations, X2 test and Fisher's exact tests. P-values < 0.05 were considered statistically significant.

Results: Mean age of the patients in months were 45 months. Male female ratio was 1.45:1. Among 65 survivors 38 (58%) showed no disability and 27 (41%) showed disability. Infections emerged as major cause of mortality (n=23, 79%). Clinical features that showed association with mortality included hypothermia (P=0.032), hypotension (P=0.002), altered breathing pattern (P=0.0001), non reactive pupils (P=0.001), low Glasgow coma scale (GCS) (P= 0.038), hypotonia (P=0.002), hyporeflexia (P =0.0001) and muscle power score of two (P=0.043).

Conclusion: Infections were the leading cause of non-traumatic coma as well as the leading cause of mortality in our study. Hypothermia, hypotension, altered breathing pattern, non reactive pupils, low GCS, hypotonia, hyporeflexia and low muscle power score were significantly associated with mortality in children presenting with non-traumatic coma.

Keywords: Non-traumatic coma, Children, Mortality (JPMA 61:671; 2011).

Introduction

Non traumatic coma (NTC) in children is a common cause of admission in paediatric emergency department and is reported to carry a high morbidity and mortality.[1-4] Various etiological factors have been identified for NTC, however considerable regional diversity exists in these etiological factors with infectious problems suggested to be more common in developing countries.[5] The data from developing countries is limited to a few case series and as such these suggestions cannot be generalized until more such series are reported from several different areas. Outcomes of coma is also difficult to predict early in the course of illness and despite its prevalence and associated poor outcomes, very little information is available from the literature especially from developing countries.[1,5-8] Although many studies showing prognostication parameters of coma are available in adults, limited reviews are available for children.[2]

In order to improve outcome in these patients, it is imperative that the problem be studied in a more comprehensive manner. This requires studying the common etiologies of NTC in specific regions as well as studying clinical features and laboratory parameters that may be identified early in the course of disease in order to assist in the prediction of poor outcome. A comprehensive literature search failed to reveal any such study done on children in Pakistan, so far in this regard. The current study was undertaken in an attempt to fill this void by identifying common etiologies of NTC in Pakistani children and also by identifying possible predictors of morbidity and mortality in these patients.

Patients and Methods

Coma was defined as the 'unintentional failure of the patients to open their eyes spontaneously or in response to noise, inability to obey commands or localize painful stimulus with or without the ability to express comprehensible words or age appropriate language responses.[3] We included all patients aged 2 months to 14 years presenting to the emergency room with less than seven days history of coma and without a preceding history of trauma. Children with neuro-developmental delay, those with pre-existing neurological illness such as cerebral palsy and those in whom the outcome could not be determined due to lack of follow up, were excluded.

Study was conducted after approval from hospital ethics review committee and sample was drawn form a single unit of a tertiary care university hospital in Karachi, Pakistan. Cross-sectional study design with systematic random sampling technique was adopted and one hundred patients were enrolled and followed for the study duration. Data was collected over one year period, from February 2008 to February 2009, on every third and sixth day of the week, as this is the frequency at which patients are admitted in the paediatric unit where the study was conducted. A single researcher (SS) collected the demographic data by interviewing the patients' parents and kept record of the laboratory and radiology workup. Clinical features and laboratory data were collected at the time of admission. Coma was classified into groups based on etiology, which are mentioned in Table-1. Hypoglycemia, hypocalcemia and hyponatremia were grouped in the metabolic group while congenital hydrocephalus, a-genesis of corpus callosum and schizencephaly formed the congenital malformation group. Certain laboratory investigations which were done in all patients comprised of complete blood count, electrolytes, blood sugar levels, urine analysis, stool analysis, chest X-rays and bacterial blood culture, special laboratory tests that were done in certain cases included cerebral-spinal fluid (CSF) microscopy and bacterial culture, microscopy or ICT test for malaria, Mantoux test, tuberculosis culture and PCR-T.B done on gastric aspirate and CSF, brain imaging studies and Electro encephalogram (EEG). In cases where PCR for herpes simplex were negative ,viral encephalitis was diagnosed on basis of either suggestive CSF or suggestive CT brain and EEG report, similarly when PCR was negative for tuberculosis meningitis, erythrocyte sedimentation rate (ESR), chest x-ray and positive family history were used for diagnosis. All the lab investigations were done through hospital funds for the poor and patients did not bear the cost. Outcomes were classified as survived, expired, referred or lost to follow up. Among those who survived, outcomes were further classified in terms of presence or absence of disability. Disability was defined as presence of motor or neurological deficit.

Data was entered using double data entry method and analyzed with SPSS version 16. Descriptive statistics were generated for all variables. Relationships between categorical variables were evaluated by examining cross-tabulations, X2 test and Fisher's exact tests. All P-values were two-sided and $P < 0.05$ was considered statistically significant.

Results

One hundred and eleven patients fulfilled the inclusion criteria over the study period, of which eleven were later excluded due to various reasons leaving a final sample size of one hundred patients. Mean age of our patients was 44 ± 45 months. Forty (40%) patients were less than 1 year of age, 35 (35%) between 1 and 5 years and 25 (25%) older than 5 years. Fifty nine were males and forty one female, giving a male to female ratio of 1.45:1. Etiological breakup of patients is mentioned in Table-1, out of 20 cases of bacterial meningitis cultures were positive for nine patients and all showed Streptococcus Pneumoniae, cultures for all the cases of viral encephalitis and tuberculosis turned out to be negative. Malaria was positive in all the cases, out of 19 eleven were caused by P.Falciparum, five were mixed infections and three were caused by P.Vivax. Metabolic causes of coma were identified in six cases, five were due to hypoglycemia. Laboratory workup is mentioned in Table-3. Only 29 children underwent neuro-radiological workup through CT and/or MRI scan the findings of which are mentioned in Table-4.

Table-1: Etiology of coma in study population.

Classification	Diagnosis	Frequency/Percentage
Infective Causes	Acute Bacterial Meningitis	20(31%)
	Viral Encephalitis	12(18%)
	Cerebral Malaria	19(29%)
	TB Meningitis	8(12%)
	Sepsis	5(8%)
	Reye's Syndrome	1(2%)
	Total	**65**
Non-infective causes	Metabolic Derangements	9(26%)
	Accidental Poisoning	5(15%)
	Epilepsy (other than febrile fit)	5(15%)
	Diagnosis Not Made	4(11%)
	Neoplastic	3(9%)
	Febrile Fit	2(6%)
	Hypertensive Encephalopathy	2(6%)
	Congenital Malformation	2(6%)
	Miscellaneous	2(6%)
	Total	**34**

The final disposition of the patients was; 65 were discharged after full recovery, 29 expired, four left against medical advice while two were referred to other centers due to logistic issues. Long term outcomes was analyzed on the 65 survivors out of which 38 (58%) showed no disability and 27 (41%) showed neurological or motor disability. No significant statistical relation between the etiology and disability could be determined. Twenty six (40%) of the survivors arrived in the emergency room within 48 hours of onset of coma, 17 (26.2%) arrived after a delay of 3-5 days and 22 (33.8%) arrived after 5 days.

On further analysis of patients who expired, infections emerged as major cause of mortality (n=23, 79%), followed by metabolic causes (n=6, 20%). Predictors

Table-2: Clinical features of study patients and their association with the outcome.

Variables	Values	N	Comparison with outcome		
Vital Signs			**Survived**	**Expired**	**P-Value**
Temperature on admission	Afebrile	24	18(75%)	6(25%)	0.032*
	<96 oF	37	18(48.6%)	19(51.4%)	
	>100 oF	39	29(74.4%)	10(25.6%)	
Heart rate on admission	Bradycardia	47	26(55.3%)	21(44.7%)	0.12
	Normal	20	16(80%)	4(20%)	
	Tachycardia	33	23(69.7%)	10(30.3%)	
Respiratory rate on admission	Normal	53	39(73.6%)	14(26.4%)	0.138
	Increased	34	18(52.9%)	16(47.1%)	
	Decreased	13	8(61.5%)	5(38.5%)	
Systolic blood pressure on admission	Increased	10	6(60%)	4(40%)	0.018*
	Normal	42	33(78.6%)	9(21.4%)	
	Decreased	45	26(57.8%)	19(42.2%)	
	Unrecordable	3	0(0%)	3(100%)	
Diastolic blood pressure on admission	Increased	17	12(70.6%)	5(29.4%)	0.002*
	Normal	49	38(77.6%)	11(22.4%)	
	Decreased	29	15(51.7%)	14(48.3%)	
	Unrecordable	5	0(0%)	5(100%)	
GCS	3	9	3(33.3%)	6(66.7%)	0.038*
	8-Apr	46	28(60.9%)	18(39.1%)	
	9 and above	45	34(75.6%)	11(24.4%)	
	Examination finding				
Respiratory pattern	Acidotic	9	3(33.3%)	6(66.7%)	0.0001*
	Cheyne Stroke	8	4(50%)	4(50%)	
	Apneic	9	1(11.1%)	8(88.9%)	
	Normal	74	57(77%)	17(23%)	
Pupillary reflex	Reactive	81	59(72.8%)	22(27.2%)	0.001*
	Non reactive	18	5(27.8%)	13(72.2%)	
Fundoscopic examination	Normal	82	56(68.3%)	26(31.7%)	0.175†
	Papilledema	18	9(50%)	9(50%)	
Cranial nerve palsy	Yes	32	21(65.6%)	11(34.4%)	1.000†
	No	68	44(64.7%)	24(35.5%)	
Muscular examination	Normal	29	24(82.8%)	5(17.2%)	0.002*
Tone	Increased	41	29(70.7%)	12(29.3%)	
	Decreased	30	12(40%)	18(60%)	
Power	1	6	4(66.7%)	2(33.3%)	0.043*
	2	18	7(38.9%)	11(61.1%)	
	3	39	25(64.1%)	14(35.9%)	
	4	22	19(86.4%)	3(13.6%)	
	5	15	10(66.5)	35(35%)	
Reflexes	Decreased	22	6(27.3%)	16(72.7%)	0.0001*
	Exaggerated	42	33(78.6%)	9(21.4%)	
	Normal	36	26(72.2%)	10(27.8%)	
Planter	Up going	26	20(76.9%)	6(23.1%)	0.1
	Down going	31	22(71%)	9(29%)	
	?Not applicable	43	23(53.5%)	20(46.5%)	
Seizure	General Tonic Clonic	36	41(65.1%)	22(34.9%)	0.371*
	Myoclonic	1	1(100%)	0(0%)	
	Focal	4	4(100%)	0(0%)	
	None	32	19(59.4%)	19(59.4%)	

*Significant with respect to cell count.
† Fisher's Exact Test.

of mortality were analyzed and it was observed that mortality was slightly higher in patients over five years of age 28% (21) compared to younger patients 32% (8) (P = 0.703), as well as in female patients as 42 (71.2%) compared to 59 male coma cases survived (p = 0.120 with X2 and 0.139 with Fisher's Exact Test). Patients' vital signs that showed any association with mortality included hypothermia, hypotension and bradycardia of which hypothermia (0.032) and hypotension (0.002) correlated significantly. Clinical features which were associated with increased risk of mortality included altered breathing pattern (P=0.0001), non reactive pupils (P=0.001), low GCS

Table-3: Laboratory and Radiological Parameters of the study sample.

Parameters Serum Tests	Normal Values Units	Findings N		Comparison with outcome Survived	Expired	P-value
TLC (n = 97)	6-15x109	Normal	49	40(81.6%)	9(18.4%)	0.002*
		Abnormal	48	25(52.1%)	23(47.9%)	
Platelet (n = 97)	150-400x109	Normal	37	24(64.9%)	13(35.1%)	0.724
		Abnormal	60	41(68.3%)	19(31.7%)	
Urea (n =92)	40	Normal	52	41(78.8%)	11(21.2%)	0.004*
		Abnormal	40	20(50%)	20(50%)	
Creatinine (n=92)	0-1 mg/dl	Normal	75	52(69.3%)	23(30.7%)	0.197
		Abnormal	17	9(52.9%)	8(47.1%)	
Sugar levels (n = 97)	60--200	Normal	89	59(66.3%)	30(33.7%)	0.828
		Abnormal	8	5(62.5%)	3(37.5%)	
SGPT (n=98)	50	Normal	66	43(65.2%)	23(34.8%)	0.724
		Abnormal	32	22(68.8%)	10(31.2%)	
PT	15	Normal	47	35(56.5%)	14(41.2%)	0.152
(n=96)		Abnormal	49	27(43.5%)	20(58.8%)	
		Radiological Study				
CT and MRI (n=33)		Normal	4	2(50%)	2(50%)	0.361
		Abnormal	29	21(72.4%)	8(27.6%)	

*Significant with respect to cell count.

TLC= Total leucocyte count; SGPT= Serum Glutamic Pyrurive Transaminase; PT= Prothrombin Time; CT= Computerized Tomography; MRI= Magnetic Resonance Imaging.

Table-4: Neuro-radiological findings seen in the patients.

Radiological findings	Frequency/Percentage
Diffuse cerebral oedema	7(25%)
Intra cranial haemorrhage	5(17%)
Hydrocephalus	5(17%)
Cerebral infarction	4(14%)
Cerebral atrophy	3(10%)
Intra-axial brain tumors	3(10%)
Brain abscess	2(7%)
Total	**29**

(P= 0.038), hypotonia (P=0.002), and hyporeflexia (P =0.0001). Muscle power score of two showed significant (P=0.043) association with mortality whereas GCS score of 3 was strongly suggestive of mortality. Details of vital signs and clinical features have been shown in Table-1.

Discussion

NTC is a common presentation in paediatric patients accounting for an estimated 10-15% of all hospital admissions.[2] Despite its prevalence, associated morbidity and mortality, very little information is available from the literature, especially from developing countries.[5-8] To the best of our knowledge this is the first study from Pakistan which looks into paediatric comatosed patients and attempts to identify the common etiological factors as well as the predictors of poor outcomes in these patients. The study reveals several interesting results. We had a male to female ratio of 1.45:1 and although there is no difference in relative population of the two genders within Pakistan, especially in paediatric group, it has been previously noted that in studies reported from Pakistan that of the patients coming to the hospital, a greater proportion tends to belong to the male gender.[9] Sixty six percent of the patients had coma due to underlying infective pathologies, most notably, acute bacterial meningitis (n = 20) and cerebral malaria (n = 19). Viral encephalitis (n = 12) and tuberculous meningitis (n = 8). These findings are similar to the literature reported from other countries from the same region, although Bansal et al reported a higher frequency of tuberculous meningitis and Prabha et al reported a higher frequency of viral encephalitis.[5,7] Despite these small differences which may be attributed to sampling, it can be inferred that infective pathologies remain the prime reason for comatose pediatric patients in these countries as compared to western countries where metabolic reasons for coma are more common.[10,11]

Mortality in our study was 29%. These are encouraging statistics as the mortality of paediatric comatose patients has been estimated at 35% by a study from India where the patient demographics are comparable to our, and at around 25% by studies from other countries.[5,6,12] In our study 27(41%) children showed disability in acute period of illness, however, due to drop outs and lack of long term follow ups beyond one month, it was difficult to ascertain proportion of the patients who sustained long term sequel of primary disease such as seizures, hydrocephalus, cognitive and/or psychosocial problems. Within the survivors, no statistically significant association between the etiology of coma and probability of disability could be established .We noticed an alarming delay in presentation of patients to the emergency room. One would assume that with a clinical condition as obvious as drowsiness or coma, patients would be brought to the hospital earlier, however, our hospital by virtue of its location, deals primarily with patients referred from

healthcare facilities in rural areas, which may take up to a week at times. A direct relationship could be observed between delay in presentation and eventual outcome as survival was maximum 26% (17) in children who came to the hospital within 48 hours of onset of illness.

Among the patients' vital signs recorded at the time of arrival in the emergency room, the comparison of the vital signs of the patients with outcome showed hypothermia and, hypotension to be significantly associated with mortality, whereas bradycardia did not, although it was observed in as many as 47% of patients, of which 44.7% expired. Hypothermia and hypotension, representing circulatory instability have also been implicated by other investigators as an indicator of poor outcome and although Bansal et al found a similar association for bradycardia, to the best of our knowledge these are the only two papers that have come across this finding.[5,13] Fever, hypertension or tachycardia did not correlate with poor outcome. Clinical features which showed significantly increased association with eventual mortality include altered breathing pattern especially acidotic or apneic breathing (P=0.0001), non reactive pupils (P=0.001), low GCS (P=0.038), hypotonia (P=0.002), and hyporeflexia (0.0001). These findings have also been suggested by previous investigators and our study further validates their conclusions.[5-7,13] Most patients presented with a Glasgow Coma Score (GCS) ranging from 4-8 and a GCS of three was strongly suggestive of mortality (p=0.038), a finding also supported by other studies.[14,15] Muscle flaccidity showed significant (P=0.043) association with mortality, a finding that may validate the previous observation that motor score of GCS may be a significant independent predictor of poor outcome.[15] Similarly, factors such as papilloedema, cranial nerve palsies, abnormal plantar response (in patients older than one year), and a history of seizures did not correlate with poor eventual outcomes. None of the laboratory parameters showed any association with mortality.

Although appropriate statistical tests were applied to minimize error, this remains a cross sectional study with a small sample size. The findings of this study cannot be generalized on the whole paediatric population of Pakistan or even Karachi, but it has certainly provided an interesting overview of the problem.

Conclusion

Infections were the leading cause of non-traumatic coma as well as the leading cause of mortality in our study. Hypothermia, hypotension, altered breathing pattern, non reactive pupils, low GCS, hypotonia, hyporeflexia and low muscle power score were significantly associated with mortality in children presenting with non-traumatic coma.

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