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Pattern of neurological dysfunctions in pediatric intensive care unit

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Abstract. The aim of this retrospective study is to evaluate the burden, characterize the demographics and visualize the final outcome of the critical neurological cases admitted to a tertiary pediatric intensive care unit in Cairo University Children Hospital. Data of 139 pediatric critical care patients admitted with neurological dysfunction were reviewed, retrospectively. Patients with critical neurological illness represented 30% of the total admissions (n = 139). Coma patients (n = 115, 83%) were divided into structural/intrinsic coma (n = 54, 47%) and metabolic/toxic (n = 61, 53%). Patients with neuromuscular disorders comprised 17% (24/139) of the cohort. Patients with toxic/metabolic coma had higher Pediatric Risk of Mortality scores, higher inotrope scores, more organ system failures, a higher percentage of pre admission cardiac arrests and higher frequency of septic shock diagnosis. Predictors of death in the whole group included (a) Number of organ failure: patients with three or more organ systems failure were 3.1 times more liable to die (b) Glasgow Coma Scale (GCS): cases with GCS score less than eight were 4.2 times more prone to die, (c) Those who developed acute lung injury in less than 14 days of mechanical ventilation were 10.7 times more prone to die than those who had not. Patients with toxic/metabolic coma required more intensive support giving into consideration that advanced sepsis and presence of a family member with drug addiction played a big role as an underlying cause. National programs for implementation of sepsis goal directed therapy and health awareness about the hazards of accidental drug intake are of supreme importance. Predictive factors for death in coma patients on admission were low GCS score, presence of multiple organ system failure and acute lung injury.

Keywords: Neurological dysfunction, PICU, critical pediatric patients, mortality

1. Introduction

Non-traumatic coma (NTC) in children is a common cause of admission in the pediatric emergency department and is reported to carry a high morbidity and mortality [1]. 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 [2]. Considering the fact that acute non-traumatic coma is a common problem in pediatric patients, accounting for 10-15% of all hospital admissions, it makes a heavy demand on intensive care units [3]. It is obvious that the trend of morbidities in intensive care units reflects the pattern of diseases in tertiary referral pediatric hospitals. Hence, the understanding of the pattern of morbidity in intensive care units and factors associated with mortality will enable proper planning and implementation of strategies to prevent disease and decrease morbidities. This is particularly relevant in developing countries like Egypt.

2. Materials and methods

This retrospective, observational study was conducted in the pediatric intensive care unit (PICU) of a tertiary care teaching and referral hospital over a period

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of 18 months. The study was approved by the Institutional Ethics Committee. Inclusion and exclusion criteria were as follows: All children between one month to 12 years of age, presenting with coma or neuromuscular disorders (NMD) were eligible for inclusion in the study. Cases of trauma and post-operative neurosurgical cases were excluded as they had been admitted in other centers. Demographic and clinical data were recorded at admission including Pediatric Risk of Mortality score (PRISM III), number of organ systems failure, preadmission cardiac arrest, need for mechanical ventilation, duration of ventilation, inotrope score as described by Wernovsky et al. [4]: (dopamine dose × 1) + (dobutamine dose × 1) + (adrenaline dose × 100) + (noradrenaline dose × 100) + (vassopressin dose × 100), Glasgow Coma Scale (GCS) score, convulsions, presence of increased intracranial pressure, presence of sepsis and its grade. Coma was categorized into two major groups: Structural/intrinsic or toxic/metabolic as described by Plum and Posner [5]. Those with structural/intrinsic coma included as follows: Bacterial meningitis which was defined as acute febrile encephalopathy with presence of three or more of the following abnormalities in cerebrospinal fluid (i) polymorphonuclear leukocyte > 10 cells/mm^3, (ii) glucose < 40 mg/dL or 50% of blood glucose, (iii) elevated proteins > 40 mg/dL, (iv) microorganisms seen by Gram staining. Encephalitis was defined as acute febrile encephalopathy with cerebrospinal fluid (CSF) pleocytosis with lymphocyte predominance (>5 cells/mm^3) and absence of bacteria on direct microscopy culture and where no other alternative diagnosis was identifiable. Children with coma and evidence of bleeding or isolated infarction on head imaging and no evidence of infection were labeled as having cerebrovascular disease. Brain atrophy included patients with delayed milestones of development and radiological evidence of brain atrophy. Toxic/metabolic coma included those following hypoxic cerebral injury such as after cardiorespiratory compromise, those with identified toxins by contacting the toxicology center and those with metabolic crises with suspected or proven inborn errors of metabolism. Patients with septic shock or severe sepsis presenting with acute mental changes and a cellular CSF and normal radiological diagnosis were considered as septic encephalopathy and included in the toxic/metabolic coma group.

3. Results

Neurological causes of admission to the PICU constituted 30% of the total number of patients admitted during the same period (139/468). They were further subdivided into NTC (n = 115) and NMD (n = 24). Children whose ages ranged from one to six years had the highest incidence of neurocritical illness in the study population (46%). Table 1 shows age related distribution of neurological dysfunction. The study population with coma (n = 115) were classified into the metabolic/toxic coma (61/115 or 53%) and the structural/intrinsic group (54/115 or 47%). Table 2 shows the study population with coma according to different subclasses of coma etiologies. Septic encephalopathy (n = 28) followed by metabolic coma (n = 16) were the most common etiologies of coma in the metabolic/toxic group, while central nervous system (CNS) infections (n = 28) and cerebrovascular diseases (n = 17) were the most frequent in the structural/intrinsic group. Etiology of cerebrovascular disease was due to ischemic stroke in four patients and spontaneous intracranial hemorrhage in 13 patients. Etiology of CNS infection were meningitis (nine patients), encephalitis (15 patients), infected ventriculoperitoneal shunt (three patients) and tuberculous meningitis (one patient). Table 3 demonstrates the characteristics of the children with metabolic versus the structural coma upon the first 24 hours of PICU admission. Patients with toxic/metabolic coma were more critically and seriously ill than the structural/intrinsic group as they had more preadmission cardiac arrest (20% vs. 4%), higher median PRISM III score (13 vs. 8.5), a higher number of organ system affection (four vs. three), higher median inotrope score

Table 1
Age related distribution of neurological dysfunction

Age	Total (n = 139)		
	Structural coma n (%)	Metabolic/toxic coma n (%)	Neuromuscular diseases n (%)
1-6 months	20 (37)	15 (24.6)	1 (4.2)
7 months-1 year	7 (13)	8 (13.1)	1 (4.2)
1-6 years	22 (40.7)	27 (44.3)	17 (70.8)
More than 6 years	5 (9.3)	5 (9.3)	5 (20.8)

(20 vs. 10) and a higher incidence of septic shock diagnosis (54% vs. 24%). On the other hand, those with structural/intrinsic coma had more gross radiological abnormalities and more positive CSF findings. There were 24 patients (17.3%) who suffered from NMD on admission, these patients could be divided into two main groups; patients who are diagnosed as having Guillain-Barré syndrome, who were 19 patients (79.2% of patients with NMD), and the other group comprises patients who have other NMD, who were five patients (20.8% of patients having NMD). Table 4 shows the various etiologies for patients presenting with NMD. Out of 139 studied patients, 66 patients died during admission, with a mortality rate of 47.5% of all patients presenting with neurological dysfunction, compared to the total number of 155 patients who died during admission out of 468 patients who were admitted in the intensive care unit, with a mortality rate of (33.1%). Septic encephalopathy was the most common etiology of death among neurocritical cases (30%) to be followed by CNS infection (20%) and metabolic coma (12.3%). Table 5 shows the contribution of different diagnoses to mortality.

A multivariate analysis for death risk factors was subsequently performed using Cox Proportional Hazards Model as shown in Table 6 with a forward stepwise entry with the following co-variates: PRISM III-24, single versus multiple organ systems failure, acute lung injury, multiple organ system failure if >3 or less than three organ system failure, increased intracranial pressure, status epilepticus, the need for inotropes, presence of associated sepsis and mechanical ventilation. Using this model, the presence of three or more organ system failure (Fig. 1), GCS score less than eight (Fig. 2), and development of acute lung injury in the first two weeks of admission (Fig. 3) were found to be an independent predictor of mortality as shown in Table 6.

Table 2
The study population with coma divided into cases of metabolic or structural coma and into the different subclasses of coma etiologies

Patients with structural/intrinsic coma (n = 54)	n (%)
Cerebrovascular disease	17 (14.78)
Central nervous system infection	28 (24.35)
Brain atrophy	7 (6.09)
Other structural	2 (1.74)
Patients with toxic/metabolic coma (n = 61)	
Global hypoxic ischemic encephalopathy	6 (5.22)
Septic encephalopathy	28 (24.34)
Metabolic encephalopathy	16 (13.91)
Exogenous intoxication	7 (6.1)
Idiopathic epilepsy	4 (3.47)

Table 3
Characteristics of the children with toxic/metabolic coma versus the structural/intrinsic coma upon the first 24 hours of pediatric intensive care unit admission

Characteristics	Types of coma (n = 115)		*P* value
	Structural/intrinsic (n = 54) n (%)	Toxic/metabolic (n = 61) n (%)	
Age (yr): Median (Range)	1.0 (0.1-12)	1.0 (0.1-14)	0.324
Sex			
Male	35 (64.8)	35 (57.4)	
Female	19 (35.2)	26 (42.6)	0.415
Pediatric risk of mortality score, median (range)	8.5 (4-30)	13 (0-35)	0.021
Number of organ system failures, median (range)	3.0 (1-6)	4 (1-7)	<0.001
Pre-admission cardiac arrest	2 (3.7)	12 (19.7)	0.009
Need for mechanical ventilation	38 (70.4)	42 (68.9)	0.860
Inotrope score: median (range)	10 (0-80)	20 (0-60)	0.001
Glasgow coma scale score, median (range)	6.5 (3-13)	6.0 (3-13)	0.245
Status epilepticus	17 (31.5)	17 (27.9)	0.672
Increased intracranial pressure	43 (79.6)	30 (49.2)	0.001
Osmolar therapy	19 (35.2)	17 (27.9)	0.398
Sepsis/systemic inflammatory response syndrome	31 (57.8)	45 (73.8)	0.064
Septic shock	13 (24.1)	33 (54.1)	0.010
Gross radiological abnormalities	32 (82.1)	7 (25.0)	<0.001
Cerebrospinal fluid findings	14 (58.3)	2 (9.5)	0.025
Length of stay: median (range)	9.0 (1.0-62)	8.0 (1.0-34)	0.284
Outcome			0.055
Died	24 (44.4)	38 (62.3)	
Survived	30 (55.6)	23 (37.7)	

4. Discussion

In the current study we aimed to describe the different patterns of neurocritical illnesses observed in an Egyptian pediatric intensive care unit over an 18 month period. Most of the cases were in the age group of 1-6 years, which matches with reports about the most common age of neurocritical patients from PICUs in other developing countries. In references from Indian and Saudi Arabian hospitals, patients aged 1-5 years represented 59% and 43.9% of coma patients respectively [2,6]. Infection related coma was the most common cause of NTC in our study, as 28 patients presented with CNS infections (encephalitis n = 15, followed by meningitis n = 9 and infected ventriculoperitoneal shunt n = 3) and 28 patients presented with septic encephalopathy associated with multiple organ dysfunction syndrome. This finding emphasizes how the infectious etiology complicated by septic shock and CNS hypoperfusion is yet the prime cause of coma in our country and how much sepsis can be a burden on the economy. Wilson and Young [7], in 2003, mentioned that sepsis-associated encephalopathy is a common problem with serious consequences, hospital patients with bacteremia had abnormal electroencephalograms and 70% were diagnosed with neurologic symptoms ranging from lethargy to coma. Sepsis associated encephalopathy is recognized as the main form of encephalopathy in critically ill patients [8]. Second most important etiology of coma in our study was related to cerebrovascular disease, either in the form of stroke or spontaneous intracranial hemorrhage. Most of the patients with intracranial hemorrhage were less than six months old, suggesting that late onset hemorrhagic disease may be the cause given that they had prolonged international normalized ratio. However, the percentage was close to other studies by Bansal et al. [2] and Fouad et al. [9] who found an incidence of cerebrovascular disease; 7% and 13% respectively. The two major study groups of coma (toxic/metabolic versus structural/intrinsic) had shown statistically significant differences as regarding the parameters of severity of illness. Children with toxic/metabolic coma were more critically sick upon their PICU presentation; this could be attributed to their delayed admission from emergency departments and delayed referral from distant areas since this study was conducted in the main pediatric hospital in Egypt. Septic encephalopathy was a major contributor of this group of coma; this points to how we are still lacking early recognition and aggressive intervention for sepsis and its consequences. Pediatric studies have pointed out that the risk of death showed a twofold increase with each hour delay in the reversal of shock [10–13]. We are also used to face the obstacle of familial denial of toxic drug intake, like tramadol, and this delays hospital presentation until several hours later, when the child gets critically sick.

Table 4
Distribution of patients with neuromuscular disorders by etiology

Diagnosis	n (%)
Guillain-Barré syndrome	19 (79.2)
Smooth muscle atrophy	2 (8.3)
Dermatomyositis	1 (4.2)
Acute transverse myelitis	1 (4.2)
Undiagnosed	1 (4.2)

Table 5
Contribution of different diagnoses to mortality

Diagnosis	Total (n = 139) n (%)	Dead (n = 64) n (%)
Septic encephalopathy	28 (20)	20 (31.3)
Central nervous system infection	28 (20)	13 (20.3)
Cerebrovascular disease	17 (12)	9 (14.1)
Brain atrophy	7 (5)	2 (3.1)
Other structural	2 (1.4)	0
Global hypoxic ischemic encephalopathy	6 (4)	4 (6.3)
Metabolic encephalopathy	16 (11.5)	8 (12.3)
Exogenous toxic	7 (5)	5 (7.8)
Idiopathic epilepsy	4 (2.8)	1 (1.6)
Neuromuscular disorders	24 (17.3)	2 (3.1)

Table 6
Cox's proportional hazard models for the effect of different prognostic factors on death

Prognostic factors	Regression coefficient	Standard error	Significance	Hazard ratio	95.0% confidence interval for hazard ratio	
					Lower	Upper
Number of organ failures (<3 vs. ≥3)	1.139	0.384	0.003	3.1	1.5	6.6
Glasgow coma scale score (<8 vs. ≥8)	1.444	0.398	<0.001	4.2	1.9	9.2
Development of acute lung injury	2.373	0.464	<0.001	10.7	4.3	26.6

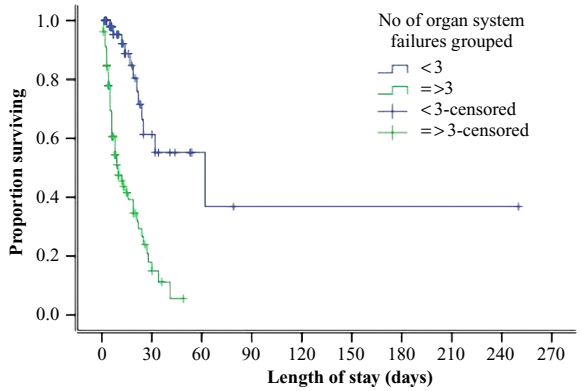

Fig. 1. Survival functions in relation to the number of organ system failures using the Cox Proportional Hazards model. The relative risk of mortality in the presence of three organ system failure was three times more than if less than three systems are involved on admission.

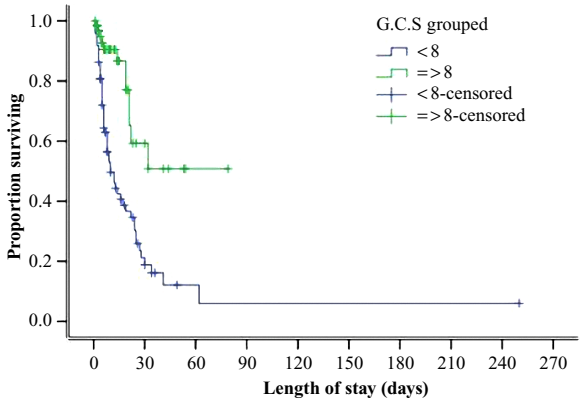

Fig. 2. Survival functions in relation to GCS scores of 8 using the Cox Proportional Hazards model. The relative risk of mortality when GCS ≥8 was 4.2. (GCS = Glasgow Coma Scale)

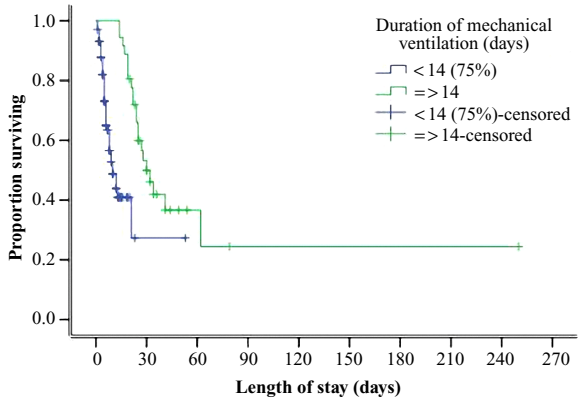

Fig. 3. Survival function in relation to development of acute lung injury in the first two weeks is associated with 10 times more death risk.

In our study, mortality of patients admitted with neurological dysfunction was 47.5% (66 patients out of 139), compared to an overall mortality rate of 33.1% of all patients admitted to our PICU during the same period. That was close to the mortality rate of neurological patients of PICUs in similar studies in Saudi Arabia by Ali et al. [6], in Egypt by Fouad et al. [9], and in Nigeria by Adudu et al. [14], with mortality rates of 47.5%, 50% and 52.4%, respectively. Septic encephalopathy and CNS infection were the major causes of deaths in our study, to be followed by the cerebrovascular diseases. However, in a study from India by Nayana Prabha et al. [15] the mortality was higher in the metabolic group (48%) and the mortality in intracranial infections and encephalopathies was 36.6% and 30.5%, respectively. In the study by Bansal et al. [2] infectious etiology resulted in the highest death rate, followed by toxic/metabolic etiology.

The most important predictor of death was a GCS score less than eight, which was associated with increasing risk of death 4.2 times. This finding is similar to other studies. Ahmed et al. [16] reported increased mortality with low GCS while Chaturvedi et al. [17] mentioned a significant association between death and modified GCS scores on admission with a posttest probability for discharge being only 10% with a score of less than five and 99% with a score of more than 10. Development of acute lung injury in the first two weeks had a 10.7 risk of death. Causes of pulmonary dysfunction in patients with head injury include pneumonia, aspiration and pulmonary embolism. Acute lung injury occurs in 20% of patients with isolated brain injury and is associated with a poor outcome; hypoxemia represents a secondary insult associated with a poor outcome [18]. It is the prevailing view that the autonomic response to elevated intracranial pressure plays an important role in the pathogenesis of neurogenic pulmonary edema. However, what occurs mechanistically at the level of the pulmonary vascular endothelium remains enigmatic and theoretical. Several clinicopathologic paradigms have been proposed to explain the clinical syndrome of neurogenic pulmonary edema: Neurocardiac, neurohemodynamic; “blast theory” and pulmonary venule adrenergic hypersensitivity [19]. But there are not any pediatric studies on outcome of acute lung injury following neurocritical illness.

In our study, 24 out of 139 studied patients (17.3%) presented with NMD. Out of these 24 patients, two patients (8.3%) died; one of them was diagnosed with spinal muscular atrophy, the other patient diagnosed

with Guillain-Barré syndrome (5.2% of patients having Guillain-Barré syndrome). Regarding age group distribution, Sarkar et al. [20] mentioned that 51% of their patients presented between the age of 6 to 10 years, and only 19.4% between 1 and 6 years of age, compared to 20.8% and 70.8% in these age groups respectively in our study [20].

This study clearly describes that neurocritical illness has a significant contribution to the mortality rate in PICUs. It also indicates that some of the etiological factors are preventable as the application of goal directed therapy in septic shock management and community orientation about the hazards of accidental drug intake. Toxic/metabolic coma patients were sicker upon PICU presentation and early aggressive support for the associated multiple organ system affection, and more precise neuromonitoring might improve their outcome.

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