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Original Article

Short term Neurological Complications After Surgical Correction in Children with Congenital Heart Disease: A Single Center Study

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Abstract:
Background: Congenital heart disease represents a common type of birth defects. Cardiac surgery required for correction of these congenital anomalies may result in multiple neurological complications during or after surgery either transient or permanent.
Aim of the Work: To determine the frequency and the outcome of the short term neurological complications in children undergoing congenital heart disease surgery.
Patients and Methods: An observational prospective study was conducted in the postoperative cardiac Pediatric Intensive Care Unit (PICU) in Cairo University Children Hospital. It included 105 patients from 1 month to 12 years who underwent surgery for correction of the congenital heart disease. Follow up of the patients who developed neurological complications for 3 months post discharge from PICU was done to assess the outcome.
Results: 16 patients (15.2%) developed acute neurological complications. Seizures were in 11 patients, 3 of them had associated disturbed conscious level (DCL) and stroke. Delayed recovery of consciousness was found in 6 patients, 5 of them were associated with seizures. Intensive care unit acquired weakness (ICUAW) was reported in 5 patients. Five patients with seizures were discharged, 3 of them with regressive course post discharge where seizures were controlled on a single antiepileptic drug (AED) and the other 2 with progressive course that necessitated addition of another AED. Four patients with ICUAW had regressive course post discharge.
Conclusion: Acute neurological complications post congenital heart diseases surgery are serious morbidities and are associated with high risk of mortality. Primary prevention of these complications by using neuroprotective measures and avoiding the development of shock, and infection beside reduction of hospital stay can be helpful in decreasing incidence of complications and improving outcome among those patients.

Level of Evidence of Study: IV (*1*)**.**
Keywords: Acute neurological complications; congenital heart disease surgery; intensive care unit acquired weakness.
Abbreviations: AED: antiepileptic drugs; AKI: acute kidney injury; CPB: cardiopulmonary bypass; CHD: congenital heart diseases; CT: computed tomography; DCL: disturbed conscious level; EEG: electroencephalography; EMG: electromyography; ICU: intensive care unit; ICUAW: intensive care unit acquired weakness; LMNL: lower motor neuron lesion; MRI: magnetic resonance imaging; NCV: nerve conduction velocity; PAB: pulmonary artery banding; PICU: pediatric intensive care unit.

Introduction

Congenital heart defects are gross structural abnormalities of the heart and the great intrathoracic vessels (*2*). They represent a common type of birth defects accounting for about one third of the all the major congenital defects (*3*). Most of these defects require surgical correction in early childhood (*4*). Advances in surgical management have led to improved survival in the patients with congenital heart disease (CHD) (*3*). Nevertheless, multiple system complications

became increasingly recognized including cardiac, pulmonary, gastrointestinal, neurological, and nephrological complications (*5*).

Neurological complications result in significant morbidity and mortality in the pediatric patients and may have a great influence on the neurodevelopmental outcome of this population. Different studies reported the occurrence of neurological complications in up to 30% of the children with CHD after cardiac surgery (*6*). The most common reported neurological complications are seizures representing about 70% 0f the cases suffering from neurological sequelae (*7*). Other neurological symptoms include altered consciousness level, critical illness polyneuropathy and myopathy, hemiparesis, organic mental syndromes, dyskinesias, gaze palsies, peripheral nerve injury as brachial plexus or phrenic nerve, and personality changes (*6*).

The aim of our study was to determine the frequency and the outcome of postoperative short term neurological complications in patients undergoing congenital heart surgery during their Pediatric Intensive Care Unit (PICU) stay and the possible risk factors predisposing to occurrence of these complications.

Subjects and Methods

This observational prospective study was carried out in the postoperative cardiac PICU in Cairo University Children Hospital over a period of 3 months (from 25/2/2019 to 25/5/2019). An informed consent was taken from the caregivers of the children with congenital heart disease undergoing a cardiothoracic surgery and admitted postoperatively to the PICU. The research was approved by the Faculty of Medicine, Cairo University Health Research Ethics Board; as abiding by The Code of Ethics of the World Medical Association (Declaration of Helsinki) for experiments involving humans (*8*).

Participants

This study included 105 patients with congenital heart disease who underwent cardiothoracic surgery and admitted postoperatively to the PICU.

Methods

The clinical data were collected in a preorganized data sheet for each patient including the age, sex, consanguinity, developmental history, past history of diseases, operations or medication, perinatal and family history of any neurological disease. Details about the cardiac illness were reviewed including the type of congenital heart disease, the type of surgery done and the intraoperative data including the duration of cardiopulmonary bypass (CPB) and aortic cross-clamp time (in minutes), circulatory arrest. Any detected neurological complications during their PICU stay (seizures, altered sensorium, muscle weakness abnormal movements and stroke) were documented. Follow up of the patients who suffered the neurological complications for three months post discharge was done for the assessment of the long term outcome.

After performing the general routine examination, the cardiac system examination was done including signs of cardiomegaly, the presence of hyperactive precordium, the presence of murmurs and their characters. Chest was examined for signs of respiratory distress, acute pulmonary edema, and infection. Neurological examination was performed including the level of consciousness, the motor system (tone, muscle power and both superficial and deep tendon reflexes), the sensory system, the cranial nerves, the gait and the coordination (whenever feasible).

The results of the routine labs requested in the ICU were retrieved including: the liver function tests, the coagulation profile, the kidney function tests, the complete blood count and the serum electrolytes. Patients suffering from the neurological manifestations included in the research underwent brain imaging either computed tomography (CT) or conventional magnetic resonance imaging (MRI) to detect the presence of any structural brain abnormality. The brain was imaged in the axial, coronal, and sagittal planes with 5 mm slice thickness. The images were interpreted by a radiology consultant who was blinded to the clinical details.

In case of seizures, interictal, artifact free, electroencephalography (EEG) using Nicolet 1 EEG system apparatus (Natus Medical, Middleton, WI, USA) was performed for at least 1 hour. The methods used to provoke abnormalities included photic stimulation. All the EEG traces were reported by a neurology consultant who was blinded to the clinical details. EEG traces were analyzed as regards the background activity, the frequency, the amplitude, as well as the occurrence of any defined abnormality such as the presence of epileptiform abnormalities in a focal or generalized distribution.

Nerve conduction velocity (NCV) and electromyography (EMG) were performed in cases of peripheral nervous system affection by a neurophysiology consultant using a Nicolet Viking Select apparatus (Natus Medical, Middleton, WI, USA). For the nerve conduction studies, surface electrodes were used. The motor and the sensory nerve conduction velocity (CV) meter/second [m/s], distal motor latency (DML) [in milliseconds], compound muscle action potential (CMAP) amplitudes [mV] and sensory nerve action potential (SNAP) amplitudes in millivolts [μV] were recorded. EMG was recorded using a coaxial needle electrode in the tibialis anterior, quadriceps femoris, abductor pollicis brevis, and deltoid muscles; additional muscles were studied in some patients.

Three months post discharge follow up was done to those patients who developed neurological complications during their PICU admission to detect the course of these complications whether the patient survived or not, the length of the hospital stay, the time required for improvement, whether complete recovery was achieved or a residual disability was present and the type and the extent of the disability.

Statistical Analysis

Data management and Statistical analysis was performed with Statistical Package for Social Science (SPSS). Numerical data were summarized using the means and the standard deviations or the medians and the ranges. Comparisons between the groups were calculated using: Student's t test & paired t tests. The categorical data were summarized as percentages, statistical differences were calculated using Chi x^2. The correlation between the variables was evaluated using the Pearson's correlation coefficient. The P-values < 0.05 was considered significant.

Results

Our study was conducted over a period of 3 months. It included 105 patients who had surgical intervention for congenital heart disease: 60 male and 45 female patients (57.1% and 42.9% of the study population respectively). The age range was from 1 month to 12 years with the median age of 9 months. Of the studied patients 69.5% suffered from acyanotic congenital heart diseases with VSD being the most common (32.3%). While the cyanotic lesions represented 30.6% of the studied patients with TGA being the most common (11.4%). Open heart surgery was done in 66.7% of the studied group while closed heart surgery was performed in 33.3% of the included patients. Corrective operations were done in 78% while palliative operations in 22% of the studied patients. VSD closure represented 35.4% of corrective operations while pulmonary artery banding represented 39.1% of those palliative operations.

Table 1. Complications in the included patients.

	Number (105)	**%**
Neurological complications	16	15.2
Regaining consciousness:		
Average (6 - 48 hour)	99	94.3
Delayed (>48 hour)	6	5.7
Seizures:		
Generalized	9	8.6
Focal	2	1.9
DCL	3	2.9
Muscle Weakness	8	7.6
Muscle tone:		
Hypertonia	3	2.8
Hypotonia	5	4.7
Reflexes:		
Hyperreflexia	3	2.8
Hyporeflexia	5	4.7
Shock	21	20
Sepsis	29	27.6
AKI	9	8.5
Coagulopathy	29	27.6

AKI: acute kidney injury.
DCL: disturbed consciousness level.

The ischemic time (the time interval between application of aortic cross-clamp to release of cross-clamp) was 10 to 120 minutes. The ischemic time was more than 41 minutes in 46 (43.8 %) patients. The CPB time (the time interval in which there is CPB that is a form of extracorporeal circulation in which the patient's blood is diverted from the heart and lungs and rerouted outside of the body) was 30 to 210 minutes. The bypass time was <1.5 hour in 72 (68.6 %) patients. The acute neurological complications occurred in 16 (15.2%) patients who underwent congenital heart disease surgery in our postoperative cardiothoracic PICU. Of them 11 (68.8%) had acyanotic congenital heart disease while the other 5 (31.2%) patients had cyanotic congenital heart disease. Seizures occurred in 11 (10.5%) patients, 9 of them had generalized seizures while the other 2 had focal seizures. Delayed regaining consciousness postoperatively occurred in 6 (5.7%) patients and disturbed conscious level (DCL) after being fully conscious postoperative occurred in 3 patients (2.9%). Only 8 (7.6%) patients had muscle weakness, five of them with signs of lower motor neuron lesion with hypotonia and hyporeflexia who were later on diagnosed as Intensive Care Unit Acquired Weakness by exclusion of other causes of muscle weakness while the other three with signs of upper motor neuron lesion with hypertonia and hyperreflexia secondary to stroke. (Table 1).

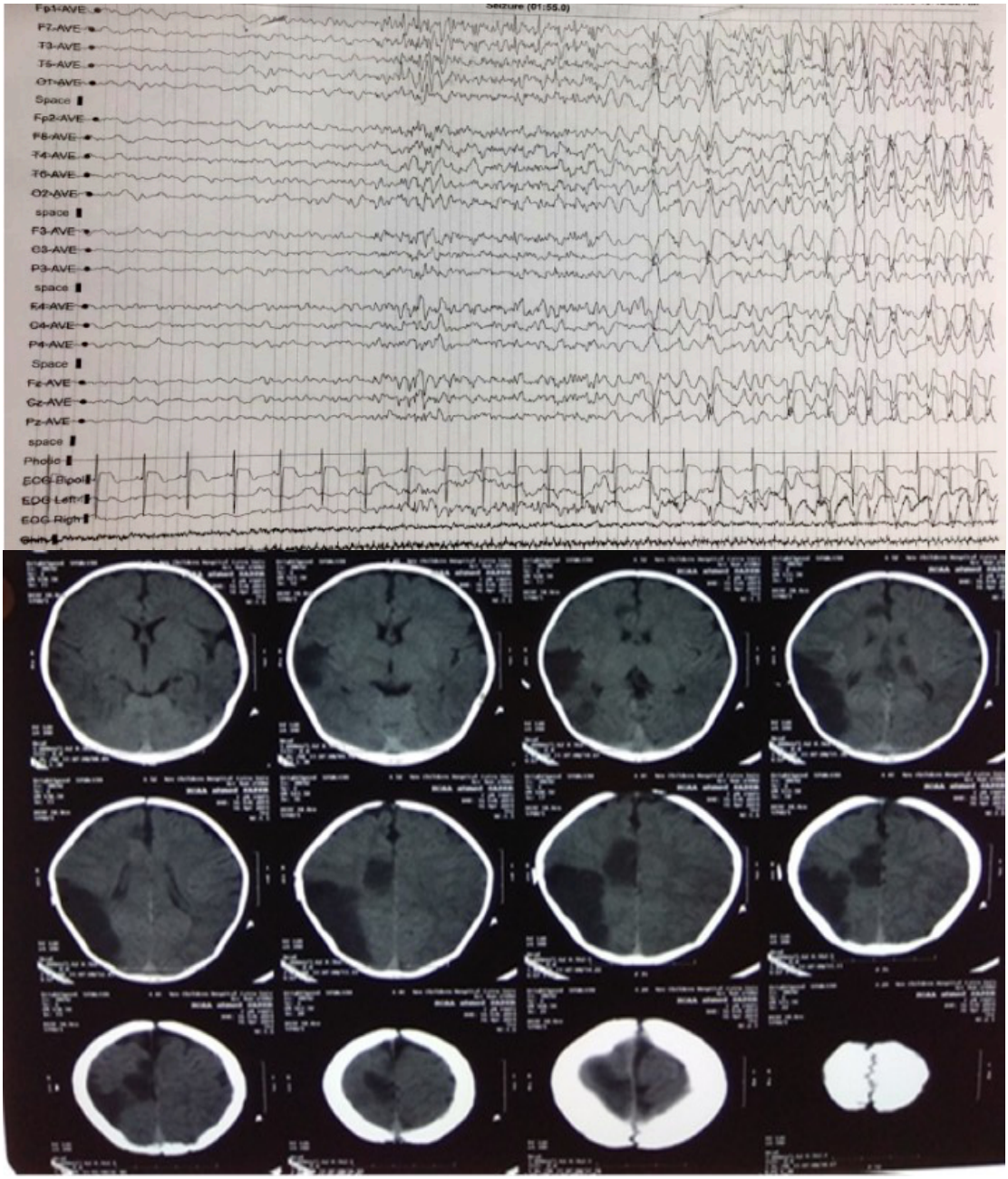

Figure 1. EEG and Non contrast CT brain of a 2 months old girl. EEG showed left frontal epileptogenic focus. CT showed left fronto-parieto-occipital and left basal ganglia ischemic insults.

Laboratory investigations showed that about 26 of the studied patients (25%) had leukocytosis, 18 patients (17%) had significant anemia, 15 patients (14.3 %) had thrombocytopenia. electrolytes disturbances reported in patients were hypernatremia in 6 patients (about 6%), hyperkalemia in 5 patients (4.7 %), hypokalemia in two patients (about 2%) and hypocalcemia in only one (1 %) of our studied patients. 9 patients (about 9 %) of the studied patient had acute kidney injury (AKI) during their ICU stay.

In the current study, seizures represented a symptom for another ongoing neurological complication in some cases. For example, it represented the main presentation of 3 patients with ischemic stroke and this was associated with DCL, shock, sepsis and impaired coagulation profile but only one of them was also associated with hypernatremia, AKI, anemia and thrombocytopenia. Combined shock and sepsis were found in four patients of those who had seizures, two of them had associated hypernatremia and thrombocytopenia while AKI was found in the other two patients. One patient of those with seizures had only shock with AKI. Rest of cases who developed seizures had no significant lab abnormalities that may explain the cause of seizures. (Table 2).

Non contrast CT brain scans were done to eight patients. Six patients of them were suffering from generalized seizures, two of them developed DCL and delayed regaining consciousness in addition to seizures. One patient had focal seizures with DCL and the last patient suffered hemiparesis. Regarding non contrast CT brain findings, ischemic stroke was found in three patients and two patients had brain edema.

EEG was done to eight of the studied patients out of eleven patients who developed seizures in ICU as the other three patients were critically ill and died before doing EEG. Positive findings were reported in four patients (3 of them had stroke), two had paroxysms of sharp slow complexes denoting a generalized epileptogenic activity while the other two had a focal spike slow complex (one of them at the left frontal "FP1, F7" area and the other one mainly at the right temporal "T4" region).

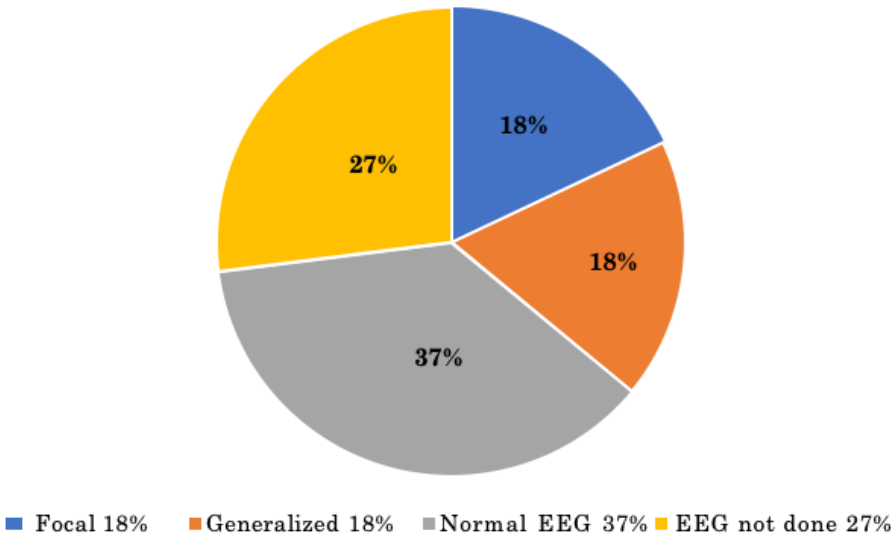

Figure 2. EEG findings in the patients with seizures.

Intensive Care Unit Acquired Weakness was reported and confirmed by EMG and NCV in 5 (4.7%) of the studied patients, four patients had axonal polyneuropathy and the last was myopathic. Two of them had VSD closure, one had common atrioventricular canal partial repair and the last one had BT shunt. The other complications encountered in the study were shock, sepsis, AKI and coagulopathy. Shock was reported in 20 % of studied patients. Regarding type of shock, 47.6 % of those who developed shock had cardiogenic shock, 38 % had septic shock and 14.4 % had hypovolemic one during their ICU stay. Sepsis was reported in 27.6 % of the studied patients. Sepsis within the first 3 days postoperative developed in 69 % of those patients and the rest 31 % of them was by the end of their first week postoperative. Nine of the studied patients (8.5%) had AKI during their ICU stay. Impaired coagulation profile was found in 29 (27.6%) patients. Regarding outcome of the congenital heart disease patients who had undergone surgery, 85.7 % were discharged from the ICU and the other 14.3 % died during their ICU stay with a mean length of hospital stay 15 days. (Figure 3).

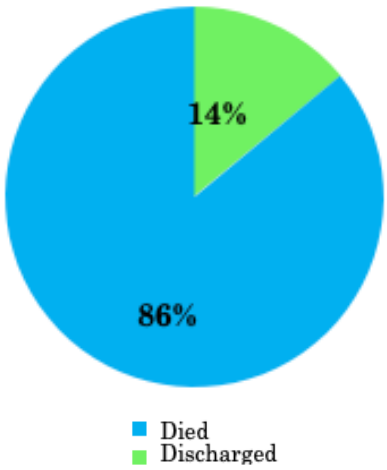

Figure 3. Outcome of the studied patients.

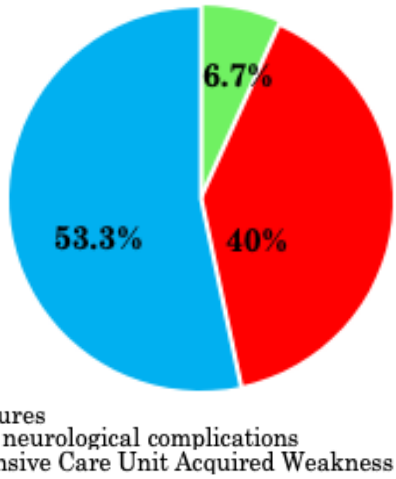

Figure 4. Neurological complications among those who died.

Among the patients who developed neurological complications in ICU, five of the eleven patients with seizures survived and the other six patients died. Two of those five had stroke out of three patients who had stroke in ICU. Four patients out of five with Intensive Care Unit Acquired Weakness (ICUAW) survived and were discharged from ICU and the other one died.

Follow up of the discharged patients with neurological complications, showed that five patients with seizures were discharged, three of them with regressive course post discharge as they were controlled on single AED and the other two with progressive course that necessitates addition of another AED. As for the patients with ICUAW they had a regressive course post discharge on physiotherapy.

Upon assessing the relation between the occurrence of different neurological complications and the clinical and laboratory variables of the patients a highly statistically significant relation was found between presence of seizure and occurrence of shock, sepsis and coagulopathy. In addition to this a significant relation between presence of seizures and low hemoglobin level, sodium level, calcium level and both highest creatinine levels, PT, PTT and INR. (Table 3).

Table 2. Relation Between Presence Of Seizures And Other General Complications.

	Seizures	P value	Stroke	P value	Muscle weakness	P value
Shock	9	<0.001	3	0.007	5	0.002
Sepsis	8	<0.001	3	0.019	7	0.259
Coagulopathy	7	<0.001	1	0.394	3	0.128
AKI	5	0.007	1	0.238	2	0.14

AKI: acute kidney injury. P <0.05 is statistically significant.

A statistically significant relation was detected between occurrence of stroke and time of regaining consciousness ($p < 0.001$). Moreover, there was a statistically significant positive correlation between the occurrence of shock and sepsis and the development of both cerebrovascular stroke and muscle weakness ($p < 0.001$). There was a significant negative correlation between presence of muscle weakness and sodium level. Also there was a significant positive correlation between the presence of muscle weakness and higher creatinine level (the group with absent muscle weakness had the lowest value) and INR (the group with absent muscle weakness had the lowest value). On the other hand, there was no correlation between presence of muscle weakness and other laboratory data.

Multivariate analysis for the factors significantly associated with acute neurological lesions showed that normal TLC, absence of shock and short average time to regain consciousness were protective factors against occurrence of neurological complications (OR=0.164, 0.091 and 0.068 respectively). (Table 4).

Table 3. Relation between presence of seizures and laboratory findings.

	Seizures		P value
	Generalized	Focal	
TLC	2.47 ± 7.68	14.85 ±7.28	0.89
Hemoglobin	11.41 ± 2.03	9.15± 2.62	0.01
Platelets	201.67 ± 119.6	184 ± 113.14	0.553
Sodium	147.67 ± 7.81	140.05± 0.71	0.018
Potassium	4.13 ± 1.07	4.2 ± 0.42	0.987
Calcium	10.51 ± 0.8	11.7± 2.97	0.047
creatinine	1.21 ± 0.74	1.5 ± 1.13	<0.001
PT	22.19 ± 8.17	27 ± 14.14	<0.001
PTT	41.38 ± 18.69	34.7 ± 1.84	<0.001
INR	1.84 ± 0.67	2.1 ± 0.99	<0.001

P <0.05 is statistically significant. INR: international normalized ratio; PT: prothrombin time; PTT: partial thromboplastin time; TLC: total leukocytic count

Table 4. Multivariate analysis of factors significantly associated with occurrence of acute neurological complications among the studied patients.

Factors	ß	P value	OR
Tlc (Normal)	-1.808	0.095	0.164
Shock (Absent)	-2.399	0.013	0.091
Mean Time to regain consciousness	-2.693	0.039	0.068

p<0.05 is statistically significant. TLC: total leukocytic count

Discussion

Acute neurological complications occurring after cardiac surgery among the congenital heart disease patients carries a great risk for both morbidity and mortality. Upon studying the risk for theses complications, we found that it occurred in 15.2% of patients who underwent congenital heart disease surgery in our postoperative cardiothoracic PICU. The risk of developing neurological events declined across the years from 32% to 4.2% among patients undergoing surgical correction of CHD (*6*, *9*, *10*). This large difference reflects the great improvement in the operative techniques over years resulting in significant decline in the neurological sequelae.

Seizures were reported as the most common neurological complication. It occurred in 10.5% of our studied patients. In the early stages after heart surgery, the most common neurological disorder manifested is seizures and its incidence after cardiopulmonary bypass was almost 4-25% (*6*, *11*, *12*). In most of the cases these seizures occurred secondary to direct surgical complications as global cerebral hypoperfusion and vascular embolization. This wide variations in the reported incidence of seizures among all studies are due to many factors as different age group of patients, preoperative patients' conditions, surgical approaches and postoperative ICU protocols.

The second most frequent neurological complication encountered in our study was the delayed regaining of consciousness postoperatively among about 6% patients. The reported delayed regaining of consciousness postoperatively occurs in about 5-8% of patients (*12*, *13*). This may occur secondary to hypoxic ischemic insult or renal impairment that may directly alter the mental state or do so by impairing excretion of sedating drugs. This may explain our report that in AKI was found in four cases of those six patients who had delayed regaining consciousness.

The occurrence of stroke with cardiac surgery is well established in adults, with an estimated frequency of 2% to 6% (*14*) while in children the reported rates are less. Cerebrovascular events were reported in 9.8% patients in our study diagnosed either clinically and/or radiologically. Lower incidence of occurrence of strokes were reported by others who reported the rate of stroke development to be 0.5 and 2.3% among all patients who underwent surgery (*10*, *12*). It occurs secondary to intracardiac and extracardiac stasis or altered vascular surfaces (*15*, *16*).

In young infants and children, stroke is less likely to be detected clinically because of the limited ability of the immature brain to manifest the focal neurologic deficits. Even diffuse neurologic damage in children with cardiac disease and cardiac surgery might be subclinical (*17*). In addition, strokes originating during or immediately following the cardiac surgery may escape the clinical recognition for several days because of the effects of postoperative sedation and

paralyzing agents. In young infants, stroke often presents with focal seizures or changes in the mental status, with the focal motor deficits being subtle. In older children, stroke usually presents with acute focal motor deficits, language disturbance, or visual dysfunction (*13*).

Critical illness neuropathy and /or myopathy documented by NCV and EMG studies was reported in 4.7% of the studied patients. It was found to be associated with the occurrence of shock and prolonged stay in the ICU and after the exclusion of hypokalemia and any previously known neuropathy or myopathy. A study conducted in Menoufia university to study critical illness polyneuropathy and myopathy reported that 28% of patients developed axonal polyneuropathy, 1.3% had demyelinating polyneuropathy, and 2.7% cases were myopathic (*18*). Many risk factors are involved in the development of CIP/CIM, such as sepsis, mechanical ventilation, prolonged immobilization, hyperglycemia, and acidosis. Early management of the severe sepsis and septic shock is also necessary. Early mobilization of the ventilated patients has been beneficial to minimize the duration of the ventilator dependence (*18*, *19*).

Acute neurological complications occurred with sepsis in the form of seizures and ICUAW were found in our study. Sepsis can lead to acute neurological complications through several mechanisms like electrolytes disturbances, AKI, multi organ affection that may increase risk of seizures and prolongation of ICU stay that rise the possibility of ICUAW (*20*).

Regarding outcome of studied patients, 85.7 % was discharged from the ICU and the other 14.3 % died during their ICU stay. About two thirds of patients with seizures were controlled on single AED and the rest required addition of another AED. This is consistent with the results of others who report that 51% - 66% of patients require single AED and 33- 49% require a second agent for seizure control (*7*, *12*).

Multivariate analysis for factors significantly associated with acute neurological lesions showed that the good prognostic factors for ICU patients after cardiac surgery were normal TLC, absence of shock and short average time to regain consciousness.

Limitations of our study include being a single center study, the small sample size and lack of MRI brain imaging.

Long term follow up of surviving patients for assessment of long term outcome is recommended. The measures suggested to overcome the high incidence of neurological complications in post cardiothoracic surgeries pediatric patients include avoidance of risk factors such as shock, infection as well as reduction of hospital stay of patients. In addition, use of intraoperative neurological monitoring using EEG and brain imaging whenever feasible aiming at early detection of neurological dysfunction and providing early intervention like cerebral dehydrating measures intraoperatively or adding drugs with neuroprotective effects in the early course of the ICU.

Conclusions

Acute neurological complications post congenital heart diseases surgery are serious morbidities and are associated with high risk of mortality. Primary prevention of these complications by using neuroprotective measures and avoidance shock, infection and reduction of hospital stay can be helpful in decreasing incidence of complications and improving outcome among those patients.

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Author Contributions

All authors searched medical literature, databases, conceptualized, conducted the case review and reviewed the final manuscript. All authors have read and agreed to the published version of the manuscript.

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CONFLICT OF INTEREST

The authors declare no conflict of interest in connection with the reported study. Authors declare veracity of information.

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