

Neurological Outcomes in Newborns with Congenital Heart Disease and Seizures

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ABSTRACT

Background: Newborns with congenital heart disease have a high risk of seizures associated with developmental delay, cerebral palsy, and epilepsy. In this study, we analyzed the etiology of seizures, electroencephalographic findings, and outcomes of newborns with congenital heart disease and seizures.

Methods: We retrospectively identified 29 newborns with congenital heart disease who presented with at least one seizure during their admission to the Neonatal Intensive Care Unit of the Hospital Italiano, Argentina.

Results: All newborns had structural/metabolic seizures. Median gestational age was 38 weeks (30-40 weeks, four pre-term) and median birth weight was 3100 g (range: 1200-4375). Neurological exam was normal in seven neonates (24%), fourteen had only one seizure, and four developed status epilepticus. The EEGs were abnormal in 21 newborns (72%). Ten showed focal paroxysms, ten showed minimal alterations with low amplitude, and one had a burst-suppression pattern. Nine newborns (31%) died due to hemodynamic decompensation. They all had an abnormal EEG ($p=0.027$) and an abnormal neurological exam ($p=0.05$), and four presented status epilepticus ($p=0.0053$). At six months, two more newborns died and two had refractory epilepsy. Of the 18 patients, six had a normal neurological exam. These 6 patients had had a normal neonatal neurological exam before hospital discharge, and four had had only one seizure. Of the six newborns, five had a normal EEG ($p=0.03$).

Conclusions: In this population, we observed a high mortality and an adverse neurological outcome. Abnormal EEG, abnormal neurological exam, and status epilepticus were significantly related to mortality.

Keywords: newborns; congenital heart disease; EEG; electroencephalogram; seizure; prognosis; outcome; epilepsy; cardiomyopathy

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BACKGROUND

Neonatal seizures are the most common clinical expression of central nervous system dysfunction in newborns and one of the most frequent neurological emergencies during this stage of life. They are usually the first sign of neurological involvement and an indicator of the risk of mortality and/or neurological sequelae. Most seizures are symptomatic; hence, the prognosis is usually poor.

The recognition of seizures in the neonatal period varies between institutions, and this may contribute to the variability in results found by different investigators. In contrast to what is seen in children and adults, seizures in neonates are rarely generalized tonic-clonic. Subtle seizures with scarce clinical manifestations are frequent. Also, electro-clinical dissociation frequently makes the diagnosis difficult. This is more marked after administering antiepileptic drugs. Such differences make it troublesome to assess the prevalence of neonatal seizures, which has been reported to be 0.5-1.4% [1,2] in term newborns and 20-25% in preterm babies.

Neonates with congenital heart disease have a high risk of cerebral lesions, seizures, and neurological impairment. By congenital heart disease, we refer to the group of congenital malformations present at birth that include cyanotic as well as non-cyanotic cardiac lesions. Their incidence is 4 to 50 per 1,000 live newborns [3, 4] and they are an important cause of neonatal morbidity and mortality. Numerous studies report a frequency of neurological sequelae of 9 to 49% [4,5]. Of those newborns, 50% will require corrective surgery.

In recent decades, advances in various corrective surgical techniques and in neonatal intensive care have improved survival rates in these children. Nevertheless, the goal of decreasing pre- and post-operative mortality, particularly that related to neurological complications, remains a challenge.

The purpose of this study is to analyze the etiology, electroencephalographic (EEG) findings, neuroimaging, and neurological sequelae of newborns with congenital heart disease who presented with seizures during their neonatal intensive care unit admission.

We were particularly interested in identifying independent predictive factors for neurological sequelae, epilepsy, and mortality in this population.

METHODS

This study is based on a retrospective, descriptive, analytical evaluation of newborns with congenital heart disease who presented with at least one seizure during their admission to the Neonatal Intensive Care Unit of the Hospital Italiano, Buenos Aires, Argentina between June 2005 and June 2011. Data was collected by reviewing the clinical charts.

A pediatric cardiologist made the diagnosis of congenital heart disease, performed the clinical assessment, and reviewed the echocardiogram and electrocardiograms.

The presence of a convulsive seizure was defined clinically by a paroxysmal event characterized by severe acute hypertonia and/or clonic or focal tonic postures that do not change with stimuli and/or the presence of a subtle seizure detected by a pediatric neurologist experienced in neonates and/or the presence of an electroencephalographic seizure demonstrated by a neurophysiologist trained in interpreting neonatal EEGs [6].

EEGs were performed within the first 48 hours of the first seizure in all newborns. Depending on infant's head size, 21 or 10 cerebral electrodes were applied according to the 10-20 International System. A technician who was present throughout the recording monitored the study. Recordings lasted 60-120 minutes in order to record periods of wakefulness and spontaneous sleep.

Two independent pediatric neurophysiologists experienced in interpreting neonatal EEG's with monopolar and bipolar montages read the EEG's. The EEG recordings were categorized according to Holmes and Lombrosos' classification [7] as: normal (organized, continuous and symmetrical without epileptiform activity), with minimal abnormalities (immature baseline rhythm, excessive discontinuous activity or mildly decreased voltage), moderate or focal abnormalities (epileptiform activity, frequency or voltage asymmetry), ictal activity (repetitive paroxysms with a clear beginning and evolution with a duration of more than 10 seconds in duration [8]), and severe abnormalities (isoelectric or markedly low voltages or a burst-suppression pattern).

A child neurologist performed the neurological exam within 24 hours of the first seizure. It was reported as normal, predominantly hypotonic, predominantly hypertonic, hemiparetic, and/or with signs of encephalopathy. At 6 months of age, the neurological assessment was repeated.

The antiepileptic drugs used were recorded as well as neuroimaging test results, i.e., transfontanelar ultrasound, computed tomography, and magnetic resonance imaging (MRI).

In accordance with ILAE guidelines, epilepsy was defined as a disorder of the brain characterized by an enduring predisposition to generate epileptic seizures [9].

Patients who presented with a congenital abnormality associated with a genetic disorder, dysmorphisms, or abnormalities in other organs were also evaluated by the genetics department.

Statistical Analysis

For categorical univariate variables, we used Fisher's test and a 2 x 2 table. A p value less than 0.05 was considered statistically significant.

Dichotomous variables (presence or absence of an abnormal neurological exam, epilepsy, and mortality) were compared with the type of congenital heart disease, Apgar score at 1 and 5 minutes, birth weight, EEG, presence of convulsive status, sex, etiology of the seizure, sepsis and mechanical ventilation.

The statistical analysis was performed with Stata software, version 8.0.

RESULTS

A total of 116 neonates who presented with at least one seizure and were hospitalized in the neonatal intensive care unit were included. Of them, 29 with congenital heart disease were analyzed. Sixteen were male (55.2%) and 13 were female (44.8%). Median gestational age was 38 weeks (30-40 weeks, 4 pre-term) and median birth weight was 3100 g (range: 1200-4375).

The incidence of neonatal seizures in the neonatal intensive care unit was 2.7%. Among the neonates with congenital heart disease, 29 (8%) had at least one seizure during hospital admission, $p=0.031$ and 20 (69%) of them had a cyanotic heart disease. The most frequent cardiac abnormality was transposition of the great vessels in 6 newborns (21%) followed by pulmonary artery stenosis in 5 newborns (17%) (Table 1).

All patients had structural/metabolic seizures. The median age at the first seizure was 11 days. In 15 neonates (52%), the seizure occurred in the context of acute hypoxia associated with hemodynamic decompensation, sepsis in

Table 1: Type of Congenital Heart Disease

Type of defect	N	%	Neonatal Mortality	Post neonatal mortality
Transposition of the Great Vessels	6	20.7%	1	1
Pulmonary Artery Stenosis	5	17.2%		1
Aortic Coarctation + VSD	4	13.8%	1	
VSD	4	13.8%	2	
LV Hypoplasia	3	10.3%	2	
Single Ventricle	2	6.9%		
ASD	2	6.9%	1	
Tetralogy of Fallot	1	3.4%		
AV Canal	1	3.4%	1	
AV Canal + Single Ventricle	1	3.4%	1	

Abbreviations: ASD: atrial septal defect; AV: atrioventricular; VSD: ventricular septal defect; LV: left ventricular

five newborns (17%), and stroke in two neonates (7%). One occurred during corrective surgery, and one was associated with a malformation of cortical development. In 5 neonates (17%), the etiology could not be determined, and the seizure was considered cryptogenic or possibly symptomatic. Abnormal findings on neurological exam were seen in 22 patients (76%). We observed hypotonia in 9 newborns (31%), hemiparesis in 6 neonates (21%), and encephalopathy or an altered level of consciousness in 6 newborns (21%) (Table 2).

While 14 neonates (48%) had a single seizure, the remaining neonates had more than one seizure. Of them, 4 (14%) presented convulsive status, and 2 neonates (7%) persisted with seizures in spite of treatment with adequate doses of antiepileptic drugs.

Treatment with phenobarbital was administered to 27 newborns (93%) as a first antiepileptic drug. As 8 newborns (27.6%) persisted with seizures, 4 (14%) received diphenylhydantoin, 3 neonates (10%) received oxcarbazepine, and 3 received (10%) benzodiazepines. Antiepileptic drugs were not indicated in 2 (7%) newborns.

Electroencephalograms were obtained in all neonates. Whereas 8 (27.6%) recordings were normal, 10 (35%) had moderate abnormalities with focal epileptiform activity, 10 (35%) had minimal abnormalities with decreased voltage activity, and one patient presented with severe abnormalities with a burst-suppression pattern.

Neuroimaging was performed in 28 newborns (97%). An MRI was performed in 17 (59%), 5 of 17 (29%) were unremarkable, 6 of 17 (35%) exhibited ischemic lesions, and 3 (18%) showed a diffuse atrophy. The other three MRIs showed hemorrhage, calcifications, and edema, respectively.

One neonate underwent brain-computed tomography, which showed atrophy, and 10 newborns underwent brain ultrasound. Among the 10 brain ultrasound exams, 7/10 (70%) were unremarkable, 2/10 (20%) showed intraventricular hemorrhage, and one had diffuse edema.

A total of 9 neonates died (31%) due to hemodynamic decompensation associated with cardiovascular failure and/or sepsis. No newborn died during a seizure. Two neonates had a left ventricular hypoplasia and two had a ventricular septal defect (Table 1). Among the patients who died, all had EEG abnormalities that were focal in 4 out of 9 newborns (44%), minimal in 4 of 9 (44%) newborns, and with a burst-suppression pattern in one. A history of convulsive status epilepticus was observed in 4 newborns (44%).

An MRI was performed in 7 of the 9 neonates. We observed ischemic lesions with involvement of borderline territories in 4 neonates (57%). One had intraventricular hemorrhage (a preterm neonate), and one had calcifications. One patient had a normal MRI.

Among the subgroup of newborns who died, 100% had an abnormal neurological exam, while such findings occurred in 65% (13/20) of the newborns who did not die, $p=0.049$ (negative predictive value: 100%). Similarly, all neonates who died had an abnormal EEG, while such findings occurred in 55% (11/20) of the neonates who did not die, $p=0.027$ (negative predictive value: 100%). We observed that 6 of 8 newborns who required the addition of a second antiepileptic drug died and only 3 of 21 neonates that required less than 2 antiepileptic drugs died, $p<0.01$.

All the patients with status epilepticus died, $p<0.01$ (positive predictive value 100%) (Table 3).

Table 2: Neurological Exam Findings

Neurological Exam		
Normal	7	24.1%
Hypotonia	9	31.0%
Hemiparesis	6	20.7%
Encephalopathy	6	20.7%
Hypertonia	3	10.3%
Dysmorphisms	7	24.1%

Table 3: Risk of Mortality

	Alive	Dead	P
Total	20	9	
Normal Neurological Exam	7	0	0.049
Abnormal EEG	11	9	0.027
Status	0	4	0.053
2 or more AEDs	2	6	0.003
Single seizure	11	3	0.180

Abbreviations: AED's: antiepileptic drugs; EEG: Electroencephalogram

On univariate analysis, the following were not associated with higher morbidity or mortality: cyanotic congenital heart disease, more than one seizure during hospitalization (excluding newborns with convulsive status), use of mechanical ventilation, history of sepsis, or gestational age of less than 37 weeks.

Outcome

At 6 months follow-up, 2 more patients died. One infant died during a hemodynamic study, and the other infant died due to an acute heart failure. Of the 18 infants, 6 (33%) had a normal neurological exam, and in all, neurological exam had been normal at the time of hospital discharge. Four of 6 (66%) had a single seizure during hospitalization, 5 of 6 (83%) had a normal EEG, and one patient presented decreased amplitude on the EEG.

Of the 12 patients with an abnormal neurological exam at 6 months of age, 1 (8%) had a normal neurological exam at discharge, $p<0.001$, and 3 of the 12 (25%) patients had a normal EEG $p=0.03$.

DISCUSSION

Newborns with congenital heart disease have an increased risk of neurological sequelae associated with a high incidence of developmental impairment and motor deficits.

Neurological status of neonates with decompensated congenital heart disease is usually abnormal [10,11], and it is not rare to find associated microcephaly and malformations of cortical development. Studies have shown that cerebral blood flow may be very low in neonates with uncorrected heart disease, demonstrating cerebral ischemia and white matter lesions consistent with periventricular leukomalacia.

Furthermore, these newborns are exposed to an increased risk of hypoxia, acidosis, and hypotension [12,13].

It is well known that seizures affect cell division and migration, receptor formation, sequential expression of receptors, synaptogenesis, and neuronal apoptosis. Such changes entail long-term cognitive consequences as well as implications for control of future seizures [6,14]. In the management of neonates with seizures, the main goal is to identify the etiology. An adequate diagnosis may lead to specific treatment, thus limiting damage to the developing brain.

Although many publications in the literature analyze the incidence of seizures, the etiologies, and semiology during the neonatal period, few studies have looked at the subgroup of neonates with CHD who presented with seizures as a neurological complication.

Among neonates with congenital heart disease, 8% presented with at least one seizure during hospital admission. Gaynor et al. reported an 11.5% when performing post-surgical 48-hour video EEG [15].

In this population, all seizures were structural/metabolic, and the main etiology was acute hypoxia secondary to hemodynamic decompensation and occasionally to sepsis. These findings agree with those of other studies, which report that about two thirds of neonatal seizures are due to hypoxic-ischemic encephalopathy [2]. Morbidity in this population is high, and 76% of newborns have abnormal neurological findings within the next 24 hours after the first seizure. At 6 months, 67% of the patients who survived had neurological sequelae. When the neurological exam and EEG were abnormal at discharge, the risk of neurological sequelae was higher.

Mortality was high; 38% of the patients died, and 81% of deaths occurred during admission.

Studies that analyzed the morbidity and mortality of term and pre-term neonates with seizures, regardless of the etiology, report similar findings: mortality 19-33%, risk of neurological sequelae: 27-67%, and normal outcome: 22-25% [16,17].

Although we found a similar mortality rate, in contrast with other series of neonatal seizures ours has a high percentage of term neonates at 86%. In this subgroup of term newborns, the mortality was 32%. Studies that assessed mortality in term neonates with seizures, regardless of the etiology, found a mortality rate of 7-9% [2,18]—less than one third of the rate in our series.

In our population of neonates with congenital heart disease, all four newborns who presented with status epilepticus died. Studies in the literature report a mortality risk of 20-35% in neonates with convulsive status admitted to the neonatal intensive care unit with various baseline diseases [2,19].

The presence of status epilepticus, an abnormal EEG, an abnormal neurological exam, and the need for more than one antiepileptic drug were associated with higher mortality. We conclude that the presence of heart disease is clearly associated with a higher mortality in newborns with seizures.

Limitations

Since the diagnosis of seizures remains clinical, it is subject to errors, either of over- or under- diagnosis. However, it is worth noting that neonatologists and nurses are widely experienced in the diagnosis of neonatal seizures. Data regarding the type of cardiovascular surgery and time on-pump were incomplete. Hence, they have not been analyzed in this study.

CONCLUSIONS

Our population of neonates with congenital heart disease had a high mortality rate, and the greatest predictors of mortality were an abnormal neurological exam, abnormal EEG, the need for more than one AED, and a history of convulsive status. Of note, the finding of a normal neurological exam during hospitalization, a normal EEG, and the presence of a single seizure was associated with a normal neurological evaluation at six months of life.

We believe that this study adds to the existing data that are predictive of morbidity and mortality in this population at risk.

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Competing interests

We (all authors) do not have any conflicts of interest in connection with the submitted article, and we did not receive any compensation for writing the article.

Author contributions

First authors who contributed equally to this work are: Marina Aberastury and Guillermo Agosta. Mentors who contributed equally to this work are: Celeste Puga, María M. Vaccarezza, Clarisa Maxit, and Walter Silva.

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