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Short communication

Epilepsy and seizures in children with congenital heart disease: A prospective study

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ABSTRACT

Purpose: Children with complex congenital heart disease (CHD) experience high incidence of perioperative seizures. Population-based studies also report high epilepsy co-morbidity in CHD. Given the increasing survival of patients with CHD and the interference of seizures and epilepsy with the long-term outcomes, characterizing them in this population is of high relevance. This study investigated the incidence and risk factors of perioperative clinical seizures (CS) and epilepsy in a prospective cohort of children with complex CHD who underwent cardiac surgery.

Methods: We included 128 consecutive children with CHD, followed for at least two years at the neurocardiac clinic of Montreal's Sainte-Justine University Hospital Center. We collected perinatal, surgical, critical care and clinical follow-up information and performed logistic regression to reveal risk factors of CS and epilepsy.

Results: Ten patients (7.8%) experienced perioperative CS. Four of them (40%) developed epilepsy. The incidence of epilepsy was therefore 3.1%. Higher surgical complexity scores, delayed sternal closure, extracorporeal membrane oxygenation (ECMO) use, longer intensive care and hospital stay were associated with CS. ECMO use and hospital stay were also associated with epilepsy. Nine (90%) patients with CS had brain injuries: five strokes, one white matter and three hypoxic-ischemic injury (HII). All patients with HII developed epilepsy, which became intractable in one of them.

Conclusion: Our study reports high incidence, surgical risk factors and brain injury patterns underlying CS and epilepsy in CHD. Further studies are needed to investigate how epilepsy interferes with neurodevelopment and quality of life in CHD.

1. Introduction

Congenital Heart Disease (CHD) is the most common birth defect. Tremendous advances in surgical techniques and intensive care have led to increased survival of patients with CHD. The research focus now shifted from survival to improving their neurodevelopment and quality of life [1,2].

Infants with CHD are at high risk of seizures. Clinically apparent seizures (CS) were reported in 4–18% of neonates during the postoperative period [3,4,8] and were linked to poor neurodevelopmental outcomes [5]. Furthermore, population-based studies show high epilepsy co-morbidity in CHD [6,7]. Seizures and epilepsy interfere with neurodevelopment and quality of life. Addressing these unexplored aspects in children with CHD is of high relevance.

We aimed to investigate the incidence and risk factors of perioperative CS and epilepsy in a prospective cohort of children with

Abbreviations: AED, anti-epileptic drugs; CPB, cardio-pulmonary bypass; CS, clinical seizure; DHCA, deep hypothermic cardiac arrest; ECMO, extra corporeal membrane oxygenation; HII, hypoxic-ischemic injury; PICU, pediatric intensive care unit; RACHS, risk adjustment for congenital heart surgery; WMI, white matter injury

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complex CHD who underwent cardiac surgery.

2. Methods

2.1. Patients

Between April 2013 and April 2016, we recruited a prospective cohort of 163 patients with CHD who underwent cardiac surgery with or without cardiopulmonary bypass (CPB) and were followed at the neurocardiac clinic of Montreal's Sainte-Justine University Hospital Center for a duration of at least 2 years.

We excluded nine patients who died, two with neurologic conditions predisposing to epilepsy (tuberous sclerosis complex and 8p23 deletion), five patients who did not undergo surgery and 19 lost to follow-up **(S1).** Those with trisomy 21 or 22q11 deletion spectrum were followed in separate clinics. A total of 128 children were included. Clinical characteristics of those excluded were not different from the entire cohort.

Demographic, perinatal, diagnostic, surgical, critical care and other clinical variables were collected from the medical charts. Perioperative seizures were defined as any CS occurring before the first surgery or less than 21 days after any surgery. Epilepsy was defined as seizure recurrence more than 21 days after the surgery.

The institutional research ethics board approved this study and parents provided written consent.

2.2. Statistical analysis

Descriptive statistics were used to characterize the groups of CHD infants with and without CS (Table 1). Frequencies (sample size and percentages) and medians with interquartile ranges (IQR) were reported for categorical and continuous variables, respectively. Univariate logistic regression was used to determine the risk factors of perioperative CS and epilepsy occurrence. Multivariable analysis was not possible due to multicollinearity. Alpha level was set to $p < 0.05$.

3. Results

3.1. CS and epilepsy characteristics

Ten patients (7.8%) experienced perioperative CS (Table 2). The median age at presentation was 5.25 months (IQR 0.2–12 months). Three patients had seizures before surgery. Two patients with genetic dilated cardiomyopathy (both TNNT2 mutations) developed strokes in the context of ventricular assisted device while waiting for their heart transplant. The third patient with a transposition of great arteries had mild white matter injury (WMI) on his brain MRI. None of them had recurrence of seizures after surgery. Seven additional patients presented with post-operative seizures (median 3 days after surgery, IQR 1–4 days): four after their first surgery, two after the second and one after his third surgery. Only three patients had EEG-confirmed seizures (S2). Three of seven experienced hypoxic-ischemic injury (HII): two in the context of extra corporeal membrane oxygenation (ECMO) and one after cardiac arrest. All patients presented with brief focal seizures and received emergency treatment with intravenous anti-epileptic drugs (AED). None experienced status epilepticus. New acquired brain injuries related to seizure etiology were found in 9/10. Maintenance treatment was started in 5/10, for a median duration of 10 months (range 6–39).

Four out of 128 patients (3.1%) developed epilepsy (median age 7.75 months, range 2–26). Seizures recurred at a median of 25.5 days (range 21–177) after surgery: all three patients with HII and one patient with Shone syndrome, the later with no MRI detected brain injury. All four patients were on maintenance therapy at seizure recurrence: two on phenobarbital and two on levetiracetam. Three patients were well controlled under AED monotherapy: two weaned off phenobarbital and one still on levetiracetam at the last follow-up. One patient with HII developed intractable epilepsy and was receiving multi-AED therapy (levetiracetam, clobazam, valproic acid and cannabidiol).

Table 1
Demographic, perinatal and perioperative characteristics in patients with and without clinical seizures.[a].

Characteristics	No CS (*N* = 118)	CS (*N* = 10)	Total (*N* = 128)	Univariate analysis *P* value
Demographic and perinatal data				
Sex, female	53 (44.9)	6 (60)	59 (46.1)	0.36
Age at first surgery, days	22 (10-121)	112 (20-187)	26 (10-131)	0.84
Gestational age at birth, weeks	38.8 (38.0-39.8)	39.0 (36.3-39.8)	38.9 (37.9-39.8)	0.69
Apgar at 5 minutes	9 (8-9)	9 (9-9)	9 (8-9)	0.36
Anatomic CHD classification[b]				0.23
Class I, *n*	90 (76)	7 (70)	97 (76)	
Class II, *n*	16 (14)	1 (10)	17 (13)	
Class III, *n*	6 (5)	0	6 (5)	
Class IV, *n*	6 (5)	2 (20)	8 (6)	
Surgical risk (RACHS) categories[c]				**0.011**
Category 1, *n*	5 (4)	0	5 (4)	
Category 2, *n*	50 (42)	2 (20)	52 (41)	
Category 3, *n*	39 (33)	3 (30)	42 (33)	
Category 4, *n*	22 (18)	1 (10)	23 (18)	
Category 5, *n*	0	0	0	
Category 6, *n*	2 (2)	2 (20)	4 (3)	
Surgical characteristics				
Cardiopulmonary bypass, min	140 (99-183)	197 (155-225)	146 (100-191)	0.06
Aortic clamp time, min	77 (39-115)	104 (86-147)	82 (41-117)	0.06
DHCA, *n*	8 (7)	2 (20)	10 (9)	0.08
Low Flow, *n*	9 (8)	2 (20)	11 (6)	0.14
Delayed sternal closure, *n*	26 (23)	7 (70)	33 (27)	**0.005**
ECMO, *n*	2 (2)	2 (20)	4 (3)	**0.013**
Postoperative complications and length of stay				
PICU length of stay, days	6 (3-10)	18 (10-102)	6 (4-10)	**0.032**
Total length of stay, days	21 (11-34)	28 (32-192)	21 (11-34)	**0.005**
Arrhythmia, *n*	12 (11)	0	12 (10)	0.99
Cardiac arrest, *n*	4 (3)	1 (10)	5 (4)	0.33
Additional cardiac surgeries (Yes/No), *n*	22 (19)	4 (40)	26 (21)	0.13

CS, Clinical Seizure; DHCA, Deep Hypothermic Circulatory Arrest; ECMO, extra corporeal membrane oxygenation; PICU, Pediatric Intensive Care Unit.

[a] Data are presented as *N* (%) or median (interquartile range).

[b] Clancy RR, McGaurn SA, Wernovsky G, et al. Preoperative risk-of-death prediction model in heart surgery with deep hypothermic circulatory arrest in the neonate. *J Thorac Cardiovasc Surg.* 2000;119(2):347-357.

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3.2. Risk factors of CS and epilepsy

Univariate analyses showed that CS were more common in patients with higher RACHS (Risk Adjustment for Congenital Heart Surgery, see Table 1) scores, delayed sternal closure and ECMO use. These patients also required longer duration of pediatric intensive care unit (PICU) and hospital stay. Patients with longer cardio-pulmonary bypass (CPB), aortic clamp times and deep hypothermic circulatory arrest (DHCA) also tended to have more CS. Univariate analyses also showed that ECMO use (OR 13.1, 95% confidence interval [CI] 1.03–165.7, $p = 0.047$) and longer hospital length of stay (OR 1.013, 95% CI 1.002–1.023, $p = 0.018$) were associated with epilepsy.

Table 2
Clinical characteristics of patients with perioperative clinical seizures.

Patterns of brain injury	Type of CHD	Stroke vascular territories or patterns of acquired brain injuries	AED on discharge, *N*	Weaned off AED, *N*	Epilepsy, *N*
Stroke (*N* = 5)	DCM	Left PCA	1	1	0
	DCM	Multiple small infarcts: left MCA, right ACA and MCA	1	1	0
	Cortriatriatum	Left MCA	1	1	0
	DORV	Right MCA	0	–	0
	HLHS	Left MCA	0	–	0
HII (*N* = 3)	AVCD	Bilateral watershed zones	0	1	1
	CoA	Bilateral BG and watershed zones	1	1	1
	TOF	Total	1	–	1
WMI (*N* = 1)	TGA	Right frontal periventricular	0	–	0
None (*N* = 1)	Shone Syndrome	No brain injury	1	–	1

ACA, anterior cerebral artery; AED, Anti-Epileptic Drugs; AVCD, AtrioVentricular Canal defect unbalanced; BG, Basal Ganglia; CHD, Congenital Heart Disease; CoA, Coarctation of Aorta; DCM, Dilated Cardiomyopathy; DORV, Double Outlet Right Ventricule; ECMO, Extra Corporeal Membrane Oxygenation; HII, Hypoxic-Ischemic Injury; HLHS, Hypoplastic Left Heart Syndrome; MCA, middle cerebral artery; PCA, posterior cerebral artery; TGA, Transposition of Great arteries; TOF, Tetralogy of Fallot; WMI, White Matter Injury.

4. Discussion

Our prospective cohort demonstrates high incidence of perioperative CS (7.8%) in children with CHD, which concords with other reports (4–18%) [3,4,8]. A recent study reported that 8% of patients undergoing cardiac surgery experience clinical and/or EEG seizures during the perioperative period [9]. In our study, EEG monitoring was not systematically performed (S2) and only one additional patient was diagnosed with preoperative EEG-only seizures. Therefore, we estimate that the actual incidence of seizures in our cohort was higher. Nonetheless, none of the patients without perioperative CS developed epilepsy. We believe that both clinical and EEG-only seizures are equally involved in epileptogenesis. However, undiagnosed and untreated EEG-only seizures persist longer and eventually manifest clinically. This underscores the importance of perioperative EEG monitoring, as seizure persistence during the critical period is one of the main predictors of later epilepsy [10].

Our study demonstrates that the main determinant of perioperative CS in CHD is the surgical treatment complexity. Higher RACHS scores, the need for delayed sternal closure and ECMO were associated with CS, and a tendency was observed for longer CPB, aortic clamp times and DHCA, which is concordant with others' reports [3,9,11]. We also revealed longer length of PICU and hospital stay in patients with CS and epilepsy. These factors are consistently associated with adverse neurodevelopmental outcomes [2], which underscores the importance of detecting and treating seizures.

Perioperative seizures in children with CHD are multifactorial in origin [10]. In our cohort, 9/10 patients with perioperative CS had new acquired brain injuries. MRI scans were not systematically performed (S2) and we could not evaluate whether brain injury was as frequent in those without CS. Still, 90% incidence is higher than the upper ranges of previously reported incidences of brain injury in CHD [1]. Further, strokes and HII, encountered in five and three patients with CS, respectively, probably play a more important role in seizure genesis than WMI, observed in only one patient, despite the fact that WMI is by far the most frequent type of injury reported in half of CHD patients. Additionally, it is also possible that delayed brain maturation characterizing children with CHD may also predispose to seizures by favoring excitatory influences [12]. Most importantly, seizures not only reflect, but also contribute to brain injury, and both are related to impaired neurodevelopment.

Our study highlights the link between perioperative CS and epilepsy. To our knowledge, this is the first prospective cohort of CHD children showing an overall incidence of epilepsy of 3.1%, but as high as 40% among those with CS over two years of follow-up.

A previous large populational cohort from Denmark reported comparable cumulative incidence of epilepsy in CHD of 5% overall, and 3% in those born at term with no extracardiac abnormalities, by the age of 15 years [6]. A population-based case–control study from UK reported 2.4% overall epilepsy prevalence in CHD compared to only 0.9% in the general population [7]. Interestingly, the risks of epilepsy decrease with age, but increase with additional surgeries [6]. It will be interesting to observe the evolution of epilepsy incidence in our cohort at five years of follow up.

Not surprisingly, our data suggest that the nature of brain lesion may be related to the risk of epilepsy. In our study, the five patients with stroke were weaned off AED and none of them developed epilepsy. Conversely, HII appears to be a risk factor of epileptogenesis. All three patients with CS and HII developed epilepsy, which became intractable in one of them. Conversely, as for the seizure genesis, WMI seems to be less epileptogenic.

5. Conclusion

Our study reports a 7.8 and 3.1% incidence of CS and epilepsy, respectively, in a prospective cohort of infants with CHD. In 90% of cases, CS were associated with structural abnormalities, most frequently stroke and HII, but only HII lead to epilepsy over two years of follow-up. Higher surgical complexity, delayed sternal closure, ECMO and longer hospital stay characterized these patients. Further studies are needed to explore the evolution of cumulative incidence of epilepsy and its developmental consequences.

Conflicts of interest

None of the authors has any conflict of interest to disclose.

Ethical publication statement

We confirm that we have read the Journal´s position on issues involved in ethical publication and affirm that this report is consistent with those guidelines.

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