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# Incidence and predictors of epilepsy in children with congenital heart disease

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**Abstract**

*Objective:* Children with CHD may be at increased risk for epilepsy. While the incidence of perioperative seizures after surgical repair of CHD has been well-described, the incidence of epilepsy is less well-defined. We aim to determine the incidence and predictors of epilepsy in patients with CHD. *Methods:* Retrospective cohort study of patients with CHD who underwent cardiopulmonary bypass at <2 years of age between January, 2012 and December, 2013 and had at least 2 years of follow-up. Clinical variables were extracted from a cardiac surgery database and hospital records. Seizures were defined as acute if they occurred within 7 days after an inciting event. Epilepsy was defined based on the International League Against Epilepsy criteria. *Results:* Two-hundred and twenty-one patients were identified, 157 of whom were included in our analysis. Five patients (3.2%) developed epilepsy. Acute seizures occurred in 12 (7.7%) patients, only one of whom developed epilepsy. Predictors of epilepsy included an earlier gestational age, a lower birth weight, a greater number of cardiac surgeries, a need for extracorporeal membrane oxygenation or a left ventricular assist device, arterial ischaemic stroke, and a longer hospital length of stay. *Conclusions:* Epilepsy in children with CHD is rare. The mechanism of epileptogenesis in these patients may be the result of a complex interaction of patient-specific factors, some of which may be present even before surgery. Larger long-term follow-up studies are needed to identify risk factors associated with epilepsy in these patients.

CHD affects 1% of births in the United States of America.[1] Medical and surgical advances have resulted in increased survival and life expectancy. This has been accompanied by recognition of short- and long-term neurodevelopmental consequences, some of which originate in the perioperative period.[2]

For example, neonates with CHD undergoing cardiopulmonary bypass are at risk of acute symptomatic seizures, with a reported incidence between 5 and 30%.[3–10] Acute symptomatic seizures have been associated with an increased length of hospital stay,[6] in-hospital mortality, and adverse neurodevelopmental outcomes, including attention deficit hyperactivity disorder,[11,12] motor impairment[9] and other developmental delays,[13] and autism.[14] While the incidence of perioperative seizures after CHD surgery has been well-described, the incidence of later epilepsy is less well-defined.

Previous studies have estimated the rate of epilepsy in patients with repaired CHD to be between 1.6 and 5.3%;[6,10,15,16] however, the majority of these studies relied on either billing codes or definitions of epilepsy that do not align with the current International League Against Epilepsy criteria for the diagnosis of epilepsy.[17] We aimed to determine the incidence of epilepsy and identify risk factors in children with CHD who underwent surgical repair using CPB.

## Materials and methods

### *Patient population*

We conducted a single-centre retrospective study of children <2 years of age undergoing CHD repair using CPB between January, 2012 and December, 2013. Patients were identified from a prospective cardiac surgery database. Only patients who were followed in the outpatient clinics at our institution for at least 2 years after their first surgery were included to ensure adequate follow-up data. For patients requiring multiple surgical repairs using CPB, data from each surgery were included. An overview of the study is shown in Figure 1.

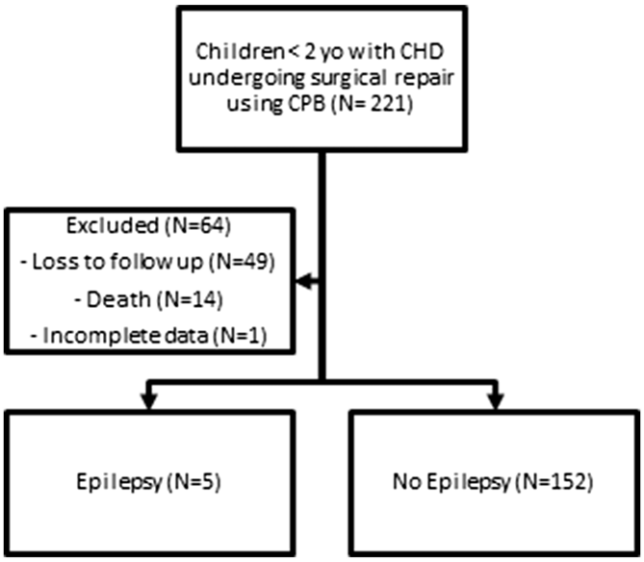


**Figure 1.** Flowchart of the Study.

### Clinical variables

Demographic and cardiac data were obtained from the cardiac surgery database. A single-ventricle defect was defined based on the Society of Thoracic Surgeons (STS) – Congenital Heart Surgery Database Committee consensus.[18] The type of CHD was also classified based on the estimated procedure-specific relative risks of mortality using the STS Congenital Heart Surgery Database and the European Association for Cardiothoracic Surgery Congenital Heart Surgery Database.[19] As per the cardiac surgery database, an operative or procedural complication was defined as a complication occurring within 30 days after surgery or other cardiac procedure (e.g., cardiac catheterisation) whether the patient was inpatient or outpatient at the time the complication arose, or after 30 days during the same hospitalisation subsequent to the operation or other procedure. Review of the electronic medical record was used to supplement the cardiac surgery data with neurologic data.

Electrographic seizures were defined as a paroxysmal EEG change that was different from the background lasting >10 seconds, with a plausible field and evolution in morphology, frequency, and spatial distribution.[20,21] Any single seizure lasting >30 minutes or recurrent seizures comprising >30 minutes of a 1-hour epoch (50% seizure burden) were considered as electrographic status epilepticus.[21–24] All EEGs were interpreted clinically by board-certified clinical neurophysiologists/epileptologists.

Seizures were classified as acute symptomatic or subacute symptomatic based on the time of occurrence after a possible inciting event: acute if the seizure onset was within 7 days or subacute if the onset was between 8 and 30 days after an inciting event.[25] An inciting event was defined as any acute CNS insult (metabolic, toxic, structural, infectious, or inflammatory) preceding the onset of the seizure.[26]

Seizures that occurred >30 days after an inciting event met the criteria for epilepsy based on the International League Against Epilepsy classification,[17] if the patient had at least two unprovoked seizures occurring greater than 24 hours apart, or one unprovoked seizure and a probability of further seizures >60%, or diagnosis of an epilepsy syndrome. A modified form of the Engel classification[27] was used to determine long-term outcome at the last follow-up visit; Class 0 = seizure-free off anti-seizure medications ≥6 months; Class 1 = seizure-free ≥6 months on medication or seizure-free off medication for <6 months, Class 2 = <1 seizure/month; Class 3 = 1–4 seizures/month; Class 4 = 5–30 seizures/month; Class 5 = >30 seizures/month. Engel classification could not be obtained in two patients with epilepsy due to insufficient information in the last follow-up visit note.

A neurodevelopmental diagnosis was obtained from chart review based on the last follow-up visit in the Neurology, Developmental Pediatrics, or Psychology clinic. We used diagnoses as assigned by the paediatric neurologist caring for the patient at the time of the diagnosis or, if the diagnosis was made by a developmental paediatrician or psychologist, a formal developmental scale, such as the Bayley Scale of Infant and Toddler Development, was used. Unfortunately, while the summative data provided in the medical record discusses the use of the Bayley to arrive at the diagnosis, the domains, cut-offs, and specific scores were not typically included in the electronic medical record.

### Neuroimaging

Imaging was obtained at the discretion of the clinical teams caring for the patient. MRI scans were performed on either a 1.5T (Discovery MR450; GE Healthcare, Waukesha, Wisconsin or Siemens Avanto, Erlangen, Germany) or 3.0T (Discovery MR750; GE Healthcare, Waukesha, Wisconsin, USA) scanner. The MRI scans consisted of T1- and T2-weighted images, susceptibility-weighted images, diffusion-weighted images, and in some cases, MR spectroscopy. If a clinically indicated MRI could not be obtained, a CT scan was performed. All MRI and CT scans were interpreted clinically by board-certified paediatric neuroradiologists.

### Data analysis and statistics

Study data were collected and managed using Research Electronic Data Capture tools hosted at the Children's National Hospital.[28] Demographics, clinical characteristics, and assessment outcomes were summarised across each group and reported with median and interquartile range for continuous variables and frequency and proportion for categorical variables. Considering the relative paucity of patients with epilepsy, Mann-Whitney U-test and Fisher's exact test were used to examine the group difference between with and without epilepsy depending on the type of variable. Due to our limited sample size in this pilot study, all the analyses are for exploratory purposes. Statistical analysis was performed using SAS for Windows version 9.4 (SAS Institute Inc., Cary, NC, USA). Two-sided test with a significance level of 0.05 was used throughout all the data analysis. This study was approved by the Institutional Review Board of Children's National Hospital (Pro00011200). Consent was not required.

## Results

Two-hundred and twenty-one patients with CHD and surgical repair using CPB were identified. Sixty-four were excluded due to loss to follow-up (n = 49), mortality (n = 14), or missing data (n = 1). A total of 157 patients were therefore included in our analysis, 5 (3.2%) of whom went on to develop epilepsy.

### Clinical characteristics

Demographic and clinical characteristics are shown in Table 1. There was no difference in sex, race, or ethnicity between patients

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**Table 1.** Clinical characteristics of patients with CHD undergoing repair using CPB with and without epilepsy

| | Total (n = 157) | No epilepsy (n = 152) | Epilepsy (n = 5) | p-value |
|---|---|---|---|---|
| *Clinical characteristics* | | | | |
| Male, n (%) | 90 (57.3) | 87 (57.2) | 3 (60) | 1.00 |
| Race, n (%) | | | | 0.28 |
| Asian | 9 (5.7) | 9 (5.9) | 0 (0) | |
| Black/African-American | 42 (26.8) | 39 (25.7) | 3 (60) | |
| Caucasian | 80 (51) | 79 (52) | 1 (20) | |
| Other | 12 (7.6) | 12 (7.9) | 0 (0) | |
| Unknown | 14 (8.9) | 13 (8.5) | 1 (20) | |
| Ethnicity, n (%) | | | | 0.44 |
| Hispanic/Latino | 21 (13.4) | 20 (13.1) | 1 (20) | |
| Non-Hispanic/Latino | 136 (86.7) | 132 (86.6) | 4 (80) | |
| Gestational age at birth, n (%) | | | | 0.08 |
| Preterm (GA<37 weeks) | 27 (17.2) | 24 (15.8) | 3 (60) | |
| Term | 123 (78.3) | 121 (79.6) | 2 (40) | |
| Unknown | 7 (4.4) | 7 (4.6) | 0 | |
| Gestational age, median in weeks (IQR) | N = 150<br>39 (37–40) | N = 145<br>39 (38–40) | N = 5<br>34 (31–38) | **0.004** |
| Birth weight, mean in kg (IQR) | N = 134<br>3.1 (2.9–3.5) | N = 129<br>3.2 (2.9–3.6) | N = 5<br>1.8 (1.6–2.7) | **0.02** |
| Single-ventricle defect, n (%) | 39 (24.8) | 37 (24.3) | 2 (40) | 0.60 |
| STS–EACTS mortality category | | | | |
| Category 1, n (%) | 31 (20.3) | 31 (20.9) | 0 | 0.58 |
| Category 2, n (%) | 31 (20.3) | 28 (18.9) | 3 (60) | 0.06 |
| Category 3, n (%) | 24 (15.7) | 23 (15.5) | 1 (20) | 0.58 |
| Category 4, n (%) | 54 (35.3) | 53 (35.8) | 1 (20) | 0.66 |
| Category 5, n (%) | 13 (8.5) | 13 (8.8) | 0 | 1.00 |
| Patients with ≥ 1 non-cardiac congenital anomaly, n (%) | 14 (8.9) | 13 (8.6) | 1 (20) | 0.20 |
| Patients with ≥ 1 chromosomal abnormality, n (%) | 37 (23.6) | 36 (23.7) | 1 (20) | 0.28 |
| Patients with a syndromic diagnosis, n (%) | 38 (25) | 37 (24.3) | 1 (20) | 0.24 |
| *Surgery data* | | | | |
| Age at the first surgery, median in days (IQR) | 78 (11–136) | 78 (10.5–134) | 55 (47–153) | 0.98 |
| Number of cardiac surgeries, median (IQR) | 1 (1–1) | 1 (1–1) | 1 (1–2) | **0.02** |
| Number of cardiac catheterisations, median (IQR) | 1 (0–2) | 1 (0–2) | 0 (0–3) | 0.82 |
| Lifetime cardiopulmonary bypass time, mean in mins (IQR) | 128 (86–196) | 127 (85–198) | 137 (98–184) | 0.71 |
| Lifetime cross-clamp time, median in mins (IQR) | N = 144<br>57 (42–80.5) | N = 139<br>58 (43–82) | N = 5<br>42 (30–56) | 0.16 |
| Lifetime deep hypothermic circulatory arrest time, median in mins (IQR) | N = 37<br>25 (8–44) | N = 36<br>26 (8–44) | N = 1<br>3 | 0.11 |
| Lifetime active cooling time, median in mins (IQR) | N = 147<br>20 (20–30) | N = 142<br>20 (20–30) | N = 5<br>27 (25–29) | 0.24 |
| *Complications* | | | | |
| Patients with cardiac complications, n (%) | 54 (34.4) | 53 (34.9) | 1 (20) | 1.00 |
| Patients with neurologic complications, n (%) | 8 (5.1) | 6 (3.9) | 2 (40) | **0.02** |
| Patients with other complications, n (%) | 21 (13.4) | 20 (13.2) | 1 (20) | 0.52 |
| Patients requiring ECMO, n (%) | 5 (3.3) | 4 (2.6) | 1 (20) | **0.03** |
| Patients requiring LVAD, n (%) | 1 (0.6) | 0 | 1 (20) | **0.03** |

(*Continued*)

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**Table 1.** (*Continued*)

| | Total (n = 157) | No epilepsy (n = 152) | Epilepsy (n = 5) | p-value |
|---|---|---|---|---|
| *Seizure data* | | | | |
| Patients with acute symptomatic seizures (any cause), n (%) | 12 (7.6) | 11 (7.2) | 1 (20) | 0.33 |
| Patients with acute symptomatic seizures (after surgery), n (%) | 2 (1.3) | 1 (0.7) | 1 (20) | 0.06 |
| Age at acute seizure onset, median in days (IQR) | N = 12<br>111 (47.2–327.4) | N = 11<br>111 (27–417) | N = 1<br>54 | 0.47 |
| *Outcome* | | | | |
| Length of hospitalisation, median in days (IQR) | 17 (7–50) | 16 (7–45) | 184 (75–191) | **0.001** |
| Developmental assessment, n (%) | 72 (45.8) | 68 (44.7) | 4 (80) | 0.12 |
| Abnormal developmental assessment, n (%) | 50 (69.4) | 46 (67.6) | 4 (100) | 0.30 |
| ID or GDD, n (%) | 26 (36.1) | 22 (32.3) | 4 (100) | **0.01** |
| Feeding difficulty, n (%) | 3 (4.2) | 2 (2.9) | 1 (25) | 0.16 |
| ADHD, n (%) | 12 (1.7) | 12 (17.6) | 0 | 1.00 |
| Isolated motor delay, n (%) | 3 (4.2) | 3 (4.4) | 0 | 1.00 |
| Autism spectrum disorder, n (%) | 5 (6.9) | 5 (7.4) | 0 | 1.00 |
| Isolated speech delay, n (%) | 4 (5.6) | 4 (5.9) | 0 | 1.00 |
| Mood disorder, n (%) | 2 (2.8) | 2 (1.3) | 0 | 1.00 |

ADHD = attention-deficit hyperactivity disorder; CBP = cardiopulmonary bypass; CHD = congenital heart disease; ECMO = extracorporeal membrane oxygenation; GA = gestational age; GDD = global developmental delay; ID = intellectual disability; LVAD = left ventricular assist device; STSEACTS = Society of Thoracic Surgeons Congenital Heart Surgery Database and the European Association for Cardiothoracic Surgery Congenital Heart Surgery Database.
P-values marked with bold indicate statistically significant differences between the groups.

with and without epilepsy. Although equivalent numbers of patients were born at term and pre-term, on univariate analysis, patients with epilepsy had a lower birthweight and a lower gestational age than those without epilepsy. There was no difference in the number of patients who had non-cardiac congenital abnormalities, chromosomal abnormalities, or syndromes.

The most common CHD types in the cohort as a whole were ventricular septal defect (19%), Tetralogy of Fallot (17%), atrioventricular canal (9%), hypoplastic left heart syndrome (8%), and transposition of the great arteries (8%). Patients with and without epilepsy had similar rates of single-ventricle defects, with 25% of all patients having a functionally single ventricle.

Surgical parameters were comparable between the two groups, including age at the first surgery, number of cardiac catheterizations, and total CPB, cross-clamp, deep hypothermic circulatory arrest (if utilised), and cooling time. However, patients with epilepsy were more likely to have had a greater number of cardiac surgeries and to require extracorporeal membrane oxygenation ($p = 0.03$) or a left ventricular assist device ($p = 0.03$). Both groups experienced similar rates of cardiac and other systemic complications, with arrhythmia, delayed sternal closure, and chylothorax being most common. On univariate analysis, patients with epilepsy suffered a higher rate of neurologic complications, including arterial ischaemic stroke, although rates of acute or subacute symptomatic seizures, cerebral sinus venous thrombosis, intracerebral haemorrhage, and hypoxic-ischaemic encephalopathy were similar in both groups. Patients who went to develop epilepsy also spent a longer time in the hospital.

## Epilepsy diagnosis

The median (IQR) age at epilepsy diagnosis was 5.4 (3–51.2) months. Four patients developed focal epilepsy, while one patient had generalised epilepsy with multiple seizure types, including myoclonic and tonic seizures. Two patients had an Engel classification of 3 and one had an Engel classification of 2 at the last follow-up visit at 5.8, 7.5, and 6.4 years of age, respectively. Supplementary Table 1 summarises the clinical characteristics of patients with epilepsy.

## EEG and imaging features of patients with epilepsy

Only one patient (20%) who went on to develop epilepsy had acute symptomatic seizures; these occurred after a surgery preceded by a cardiac arrest requiring the rapid deployment of extracorporeal membrane oxygenation. This is comparable to the rate of acute symptomatic seizures in patients who did not go on to develop epilepsy (n = 11, 7.2%; $p = 0.33$). There was also no difference in the occurrence of subacute symptomatic seizures between groups. Three patients had electroclinical (n = 2) or electrographic-only (n = 1) status epilepticus, none of whom went on to develop epilepsy.

Ten patients underwent EEG monitoring after the onset of clinical acute symptomatic seizures, one of whom went on to develop epilepsy. One patient had a normal EEG, while seven had an abnormal background, either slow for age (n = 6) or discontinuous (n = 1). Other electrographic features in patients with acute symptomatic seizures are shown in (Supplementary Table 2). No EEG feature was associated with epilepsy.

Amongst the patients with epilepsy, four underwent neuroimaging in the perioperative period (Supplementary Table 1). Stroke, confirmed by CT, occurred in one patient who went on to develop epilepsy and was significantly associated with the diagnosis of epilepsy (20% versus 0%, $p = 0.03$). This occurred in the context of being maintained on extracorporeal membrane oxygenation and a left ventricular assist device for 23 and 21 days, respectively. Another patient, who had already been diagnosed

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with epilepsy, had a middle cerebral artery territory infarct diagnosed 4 years after his index surgery. The remaining patients with epilepsy had structural abnormalities but no evidence of acute injury on perioperative imaging.

### Developmental outcomes

A developmental assessment was performed in 72 patients (45.8%) at a median age of 36.2 months (IQR 30–72.7). Developmental assessments were performed at comparable rates in patients with and without epilepsy (80% versus 44.7%, p = 0.12). While 32.3% of patients without epilepsy had a global developmental delay or intellectual disability, all patients with epilepsy who had a developmental assessment (n = 4) had a global developmental delay or intellectual disability. Table 1 summarises the neurodevelopmental outcomes of children with epilepsy.

## Discussion

We found a low incidence of epilepsy in children with CHD who underwent surgical repair utilising CPB. Predictors of epilepsy included earlier gestational age, lower birth weight, a greater number of cardiac surgeries, perioperative use of mechanical circulatory support, arterial ischaemic stroke, and a prolonged hospital length of stay. Patients with epilepsy were more likely than those without epilepsy to have a global developmental delay or intellectual disability.

Our findings are in keeping with those of prior studies, which have similarly demonstrated a low rate of epilepsy in children with CHD.[6,10,15,29] In contrast to prior studies, we used ILAE criteria, which are considered as the standard definition of epilepsy, to define our incidence.[17] Ghosh et al used criteria most similar to ours, defining epilepsy as recurring seizures 30 days after cardiac surgery, and found a similar rate of epilepsy.[6] Desnous et al defined epilepsy as any seizure recurrence more than 21 days after surgery,[10] while the other prior studies did not specify the criteria used to define epilepsy.[15,29]

The predictors of epilepsy identified in our study are also similar to those seen in prior studies, including a need for ECMO,[10] acute brain injury,[6] and a prolonged length of hospital stay.[6,10] Similar to our findings, Leisner et al[15] found that the risk of epilepsy was highest amongst those who had multiple surgeries.

It is interesting that children with CHD have a low incidence of epilepsy given the high rate of brain injury and perioperative seizures in this population,[3–8,30,31] especially when taking into consideration the relatively high rate of epilepsy in other populations of children with brain injury.[25,32,33] Several factors could explain the low incidence of epilepsy in children with CHD, with the potential role of chronic tissue hypoxia being especially intriguing. For example, Zhen et al found that in rats undergoing a hypoxic preconditioning protocol, the frequency of pilocarpine-induced seizures and neuronal apoptosis was lower when compared to a group of naïve rats.[34] In addition, Xie et al showed similar effects of a high-altitude environment on the seizure threshold in a young-rat seizure model.[35] The specific mechanisms involved and clinical implications of chronic hypoxia in patients with CHD require further investigation.

Our understanding of neurodevelopmental disabilities related to CHD has evolved considerably since the inception of the Boston Circulatory Arrest Study. The earliest data from this study showed that children with TGA who underwent arterial switch operation using DHCA had poorer outcomes, manifest as an increase in acute seizures,[30] lower motor skills at 1 year of age,[36] and an increased rate of behavioural, speech, and language abnormalities by the age of 4, when compared to children who underwent arterial switch using low-flow CPB.[36] By the age of 16, patients who underwent DHCA had a higher risk of executive dysfunction, were prescribed more psychotropic medications, and had a greater need for behavioural therapies.[37] Although several additional studies have shown that a prolonged DHCA time increases the risk of acute symptomatic seizures,[5,10,31,38,39] our findings suggest that the duration of DHCA and CPB is not related to the development of epilepsy. This is in keeping with the findings of Ghosh et al[6] However, these results should be interpreted with caution given the small number of patients with epilepsy in our study.

Our findings further support emerging evidence that the mechanisms underlying neurodevelopmental disabilities and epilepsy in patients with CHD are multiple and cumulative.[40–42] Factors that may impact the risk of epilepsy include prematurity,[43,44] brain malformations,[45,46] acquired pre- and peri-operative brain injury,[6,47,48] and underlying genetic syndromes.[49,50] The disease model of epilepsy in these patients is likely to be complex and at this time is poorly understood, but is critical for the development of targeted interventions.

Ghosh et al reported that the risk of seizures is highest in the first 12 months after surgery.[6] In our cohort, three out of five patients who developed epilepsy were diagnosed within 6 months after surgery. In keeping with the findings of Ghosh et al, we found that EEG abnormalities in the acute perioperative period were not associated with epilepsy.[6] However, this must be interpreted with caution given that only 10 patients underwent EEG monitoring in our cohort. While querying a cohort who underwent surgery between 2012 and 2013 allowed for sufficient duration of follow-up to assess for the development of epilepsy, it does limit our ability to draw conclusions about the relationship between acute EEG abnormalities and the later development of epilepsy, given that EEG monitoring was not as prevalent then as it is now. At the current time, all neonates and young infants who undergo CPB at our institution have ~48 hours of continuous EEG monitoring, consistent with Naim et al[31] and the American Clinical Neurophysiology Society.[51]

Notably, all patients who developed epilepsy and had a developmental assessment had a global developmental delay or intellectual disability. As noted above, it is known that patients with CHD are at higher risk of cognitive impairment. In our study, 39.7% of our overall cohort had an intellectual disability or global developmental delay at a median of 36 months of age, similar to previous reports.[52] The increased risk of epilepsy co-occurring with higher rates of global developmental delay and intellectual disability further supports that the development of epilepsy in children with CHD is likely multifactorial, and in some patients, may be influenced more by co-occurring conditions than by the presence of CHD itself. This conclusion comes with the caveat that the diagnosis of GDD and ID was not made based on uniformly applied criteria. The diagnosis was either assigned by the paediatric neurologist caring for the patient at the time of the diagnosis or, if the diagnosis was made by a developmental paediatrician or psychologist, a formal developmental scale, such as the Bayley, was used. Unfortunately, while the summative data provided in the medical record notes use of the Bayley to arrive at the diagnosis, the domains, cut-offs, and specific scores were not typically included in the patient's electronic chart.

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Our study is further limited by the single-centre and retrospective nature of our data. Moreover, we may not have detected a subset of patients with epilepsy given that 22.2% of our cohort was lost to follow-up. Importantly, the small number of patients with epilepsy also limited our ability to perform a multivariate analysis to better identify associations between epilepsy and potential risk factors. In addition, not all data points were available for every patient in our cohort. Finally, all data come from a single institution and may not be generalisable to other paediatric centres.

## Conclusion

Epilepsy in children with CHD is uncommon. The mechanism of epileptogenesis in these patients is the result of a complex interaction of patient-specific and treatment factors, some of which may be present before surgery. Further long-term follow-up studies are needed to better delineate this risk; however, our early data can be incorporated in current comprehensive neurodevelopmental programmes to screen, identify, and treat patients with potential risk factors for epilepsy. Future directions for research on epilepsy should focus on identifying clinical, electrographic, and radiographic risk factors and understanding the temporal course of epileptogenesis in these patients.

**Supplementary material.** To view supplementary material for this article, please visit https://doi.org/10.1017/S1047951121003279.

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**Conflicts of interest.** None.

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