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A retrospective study of perioperative clinical seizures and epilepsy in children after operation for CHD

Takeshi Ikegawa[1], Shin Ono[1], Kouji Yamamoto[2], Mikihiro Shimizu[2], Sadamitsu Yanagi[1], Ki-Sung Kim[1], Yasuhiro Ichikawa[1] and Hideaki Ueda[1]

[1]Department of Cardiology, Kanagawa Children's Medical Center, Kanagawa, Japan and [2]Department of Biostatistics, Yokohama City University School of Medicine, Kanagawa, Japan

Original Article

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Author for correspondence:
S. Ono, Department of Cardiology, Kanagawa Children's Medical Center, 2-138-4 Mutsukawa, Minami-ku, Yokohama, Kanagawa, Japan.
Tel: +81-45-711-2351; Fax: +81-45-721-3324.
E-mail: sono@kcmc.jp

Abstract

This study investigated the incidence and risk factors of perioperative clinical seizure and epilepsy in children after operation for CHD. We included 777 consecutive children who underwent operation from January 2013 to December 2016 at Kanagawa Children's Medical Center, Kanagawa, Japan. Perinatal, perioperative, and follow-up medical data were collected. Elastic net regression and mediation analysis were performed to investigate risk factors of perioperative clinical seizure and epilepsy. Anatomic CHD classification was performed based on the preoperative echocardiograms; cardiac surgery was evaluated using Risk Adjustment in Congenital Heart Surgery 1. Twenty-three (3.0%) and 15 (1.9%) patients experienced perioperative clinical seizure and epilepsy, respectively. Partial regression coefficient with epilepsy as the objective variable for anatomical CHD classification, Risk Adjustment in Congenital Heart Surgery 1, and the number of surgeries was 0.367, 0.014, and 0.142, respectively. The proportion of indirect effects on epilepsy via perioperative clinical seizure was 22.0, 21.0, and 33.0%, respectively. The 15 patients with epilepsy included eight cases with cerebral infarction, two cases with cerebral haemorrhage, and three cases with hypoxic-ischaemic encephalopathy; white matter integrity was not found. Anatomical complexity of CHD, high-risk cardiac surgery, and multiple cardiac surgeries were identified as potential risk factors for developing epilepsy, with a low rate of indirect involvement via perioperative clinical seizure and a high rate of direct involvement independently of perioperative clinical seizure. Unlike white matter integrity, stroke and hypoxic-ischaemic encephalopathy were identified as potential factors for developing epilepsy.

Modifications in surgical techniques and innovations in perioperative care have improved the survival rates of patients with CHD. The focus of research is currently shifting from survival to quality of life. Seizures and epilepsy interfere with neurodevelopment and quality of life. Perioperative clinical seizures and comorbidities of epilepsy are often experienced by patients with CHD. Perioperative clinical seizure has been reported in 6–9% of neonates with CHD during the post-operative period.[1,2] Its occurrence has been associated with worse neurodevelopmental outcomes, providing an early sign of brain injury with neurological and developmental sequelae.[3] It has been demonstrated that epilepsy occurs in 2.4% of patients with CHD,[4] while another study revealed that 5% of post-operative patients with CHD develop epilepsy by the age of 15 years.[5] A single institutional retrospective study was performed to investigate the incidence and risk factors of perioperative clinical seizure and epilepsy in children with CHD.

Materials and methods

Patients

We enrolled 782 children who underwent surgery for CHD at Kanagawa Children's Medical Center (Kanagawa, Japan) from January 2013 to December 2016. The patients were followed up at our hospital for ≥4 years. Perinatal, perioperative and follow-up data were retrospectively extracted from the medical records. The onset of epilepsy was used as an endpoint, and medical data recorded after the onset were excluded. Therefore, five patients who had already developed epilepsy prior to surgery for CHD were excluded. Perioperative clinical seizures were defined as seizures that occurred within 21 days after surgery for CHD. Epilepsy was defined as a seizure that occurred >21 days after surgery and was diagnosed by a paediatric neurologist through electroencephalography. In patients with perioperative clinical seizure and/or epilepsy in whom brain imaging was performed, the findings of these analyses were retrospectively extracted from the medical records. Brain imaging involved CT and/or MRI. This study was approved by the Research Ethics Committee of Kanagawa Children's Medical Center (approval

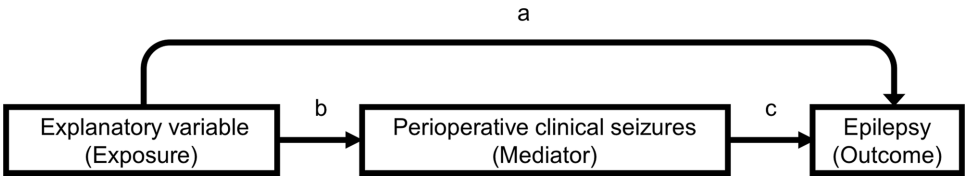

Figure 1. Proposed mediational pathway in this study Arrows indicate the flow of association. Exposure is the origin of the association of interest. The mediator was perioperative clinical seizures, a variable that may modify the exposure-outcome association. The outcome was epilepsy, an end point of this study. Pathways "a" and "bc" indicate the direct and indirect pathway from exposure to outcome, respectively.

number: 1906-12). Due to the retrospective and observational nature of the investigation, the risk associated with participation in this study was low, and it was not possible to obtain consent from each participant. Therefore, the need for informed consent was waived, and the opt-out approach was used. We published information regarding this study on the website of the Kanagawa Children's Medical Center (URL: http://kcmc.kanagawa-pho.jp/about/files/rec_circulation03.pdf). We assumed that the patients were willing to participate in this study unless stated otherwise.

Classification

Based on preoperative echocardiography, anatomical CHD classification was performed as follows: class I, biventricular circulation without aortic obstruction; class II, biventricular circulation with aortic obstruction; class III, single ventricle without aortic obstruction; and class IV, single ventricle with aortic obstruction.[6] Cardiac surgery was evaluated using Risk Adjustment in Congenital Heart Surgery 1.[7] Hence, the surgical procedure for CHD was classified into the following six stages according to the level of difficulty, regardless of the patient background. Category 1 denoted atrial septal defect surgery; category 2 denoted ventricular septal defect repair; category 3 denoted Fontan procedure; category 4 denoted atrial switch operation with ventricular septal defect closure; category 5 denoted repair of truncus arteriosus and interrupted arch; and category 6 denoted stage I repair of hypoplastic left heart syndrome (Norwood operation).

Statistical analysis

Multivariate logistic regression analysis predicted unstable estimates due to the multicollinearity and low number of events. Therefore, in this study, we constructed a regression model using elastic net[8] (a method used for the analysis of parameters). Items clinically considered to have an effect on epilepsy were used as explanatory variables. Regression analysis was performed using the elastic net method with epilepsy as the objective variable. We used two parameters (i.e. α and λ) in the elastic net model. α ($0 \leq \alpha \leq 1$) is a hyperparameter, which indicates the degree between the ridge and lasso regression. The elastic net model with $\alpha = 1$ and $\alpha = 0$ is identical to lasso regression and ridge regression, respectively. λ is a hyperparameter for the penalty term of the elastic net model. Hyperparameters are generally set by analysts. Cross-validation is frequently used to optimise the λ. In this study, we used a 10-fold cross-validation.

Subsequently, we performed a mediation analysis.[9–11] Our conceptual model is summarised in Fig 1. Perioperative clinical seizure may be the first symptom of epilepsy, and the "c" pathway of Fig 1 was presumed to be clearly correlated. Since it has been clinically predicted that perioperative clinical seizure and epilepsy are strongly associated with brain injury, it was presumed that the risk factors for perioperative clinical seizure and epilepsy overlap. In other words, it was presumed that the "a" and "b" pathways shown in Fig 1 existed. However, their individual involvement in the development of epilepsy remains unclear. Therefore, perioperative clinical seizure was considered an intermediate variable for epilepsy and excluded from the explanatory variables in the regression analysis with epilepsy as the objective variable. Mediation analysis was performed by dividing the effect of the explanatory variable on epilepsy into an indirect effect mediated by an intermediate variable (perioperative clinical seizure) and a direct effect not mediated by this variable. All statistical analyses were conducted using R version 4.0.2 (R Core Team, 2018). We used the glmnet package[12] in the analysis with the elastic net model mediation analysis and the mediation package[13] in the mediation analysis. The significance level was set at p-values <0.05.

Results

Perinatal and perioperative characteristics of patients with and without epilepsy

Table 1 shows the characteristics of patients in the epilepsy and control groups. Of the 777 patients, 15 (1.9%) and 23 (3.0%) experienced epilepsy and perioperative clinical seizure, respectively. Ten of the 15 patients (66.7%) who developed epilepsy also experienced perioperative clinical seizure. Among those who used extracorporeal membrane oxygenation less than 7 days after surgery (15 patients), three (20.0%) had epilepsy and one (6.7%) expired without withdrawal from extracorporeal membrane oxygenation. In patients who used extracorporeal membrane oxygenation ≥7 days after surgery, there was no occurrence of epilepsy, and eight of nine (88.9%) patients expired without withdrawal from extracorporeal membrane oxygenation.

Elastic net

Anatomical CHD classification, Risk Adjustment in Congenital Heart Surgery 1, post-operative extracorporeal membrane oxygenation use, number of surgeries, and delayed sternal closure were used as explanatory variables. The results of the analysis performed with the elastic net method using the explanatory variables and epilepsy as the objective variable are shown in Table 2.

The partial regression coefficient with epilepsy as the objective variable for anatomical CHD classification, Risk Adjustment in Congenital Heart Surgery 1, and the number of surgeries was 0.367, 0.014, and 0.142, respectively. These findings showed that epilepsy was more common in patients with higher anatomical CHD classification, higher Risk Adjustment in Congenital Heart Surgery 1, and higher number of surgeries.

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Table 1. Perinatal and perioperative data of patients with and without epilepsy

	Total		No epilepsy		Epilepsy		Univariate analysis
	n = 777		n = 762 (98.1%)		n = 15 (1.9%)		p-value
Perinatal data	n	%	n	%	n	%	
Sex							0.699
Male	428	55.1	419	55.0	9	60.0	
Female	349	44.9	343	45.0	6	40.0	
Gestational age at birth							0.370
<37 weeks	134	17.2	133	17.5	1	6.7	
≥37 weeks	613	78.9	599	78.6	14	93.3	
Missing data	30	3.9	30	3.9	0	0.0	
Gestational weight at birth							0.808
<1000 g	42	5.4	42	5.5	0	0.0	
≥1000 g, <1500 g	21	2.7	21	2.8	0	0.0	
≥1500 g, <2500 g	177	22.8	173	22.7	4	26.7	
≥2500 g, <4000 g	499	64.2	488	64.0	11	73.3	
≥4000 g	4	0.5	4	0.5	0	0.0	
Missing data	34	4.4	34	4.5	0	0.0	
Fetal diagnosis	307	39.5	298	39.1	9	60.0	0.101
Chromosome/gene abnormality	157	20.2	155	20.3	2	13.3	0.503
Anatomic CHD classification							<0.001
Class I	591	76.1	587	77.0	4	26.7	
Class II	67	8.6	66	8.7	1	6.7	
Class III	79	10.2	74	9.7	5	33.3	
Class IV	40	5.1	35	4.6	5	33.3	
Perioperative data							
RACHS-1							<0.001
Category I	144	18.5	144	18.9	0	0.0	
Category II	250	32.2	249	32.7	1	6.7	
Category III	305	39.3	296	38.8	9	60.0	
Category IV	55	7.1	54	7.1	1	6.7	
Category V	0	0.0	0	0.0	0	0.0	
Category VI	23	3.0	19	2.5	4	26.7	
Post-operative ECMO use	24	3.1	21	2.8	3	20.0	<0.001
Number of deaths*	9	1.2	9	1.2	0	0.0	
Post-operative ECMO duration							
<7 days	15	1.9	12	1.6	3	20.0	
Number of deaths*	1	0.1	1	0.1	0	0.0	
≥7 days	9	1.2	9	1.2	0	0.0	
Number of deaths*	8	1.0	8	1.0	0	0.0	
Number of surgeries							<0.001
1	590	75.9	584	76.6	6	40.0	
2	130	16.7	126	16.5	4	26.7	
3	40	5.1	36	4.7	4	26.7	

(*Continued*)

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Table 1. (*Continued*)

	Total		No epilepsy		Epilepsy		Univariate analysis
	n = 777		n = 762 (98.1%)		n = 15 (1.9%)		p-value
4	13	1.7	12	1.6	1	6.7	
5	4	0.5	4	0.5	0	0.0	
Delayed sternal closure	48	6.2	45	5.9	3	20.0	0.025
Perioperative clinical seizure	23	3.0	13	1.7	10	66.7	<0.001

ECMO = extracorporeal membrane oxygenation; RACHS-1 = Risk Adjustment in Congenital Heart Surgery 1.
*Number of deaths without withdrawal from ECMO after surgery for CHD.

Table 2. Analysis using the elastic net method with epilepsy as the objective variable

Explanatory variable	Partial regression coefficient
Intercept	−4.50894819
Anatomic CHD classification	0.367
RACHS-1	0.014
Post-operative ECMO use	–
Number of surgeries	0.142
Delayed sternal closure	–

ECMO = extracorporeal membrane oxygenation; RACHS-1 = Risk Adjustment in Congenital Heart Surgery 1.

Table 3. Mediation analysis with perioperative clinical seizures as the mediator and epilepsy as the outcome

		95% CI		
Association	Estimate	Lower	Upper	p-value
Exposure, anatomic CHD classification				
Natural direct effect	0.004	−0.001523	0.010	0.076
Natural indirect effect	0.002	−0.002017	0.010	0.246
Total effect	0.006	−0.000662	0.010	0.056
Proportion mediated	22.0%	−0.710595	1.070	0.236
Exposure, RACHS-1				
Natural direct effect	0.002	−0.00723	0.010	0.200
Natural indirect effect	0.001	−0.00324	0.010	0.460
Total effect	0.003	−0.00671	0.010	0.170
Proportion mediated	21.0%	−2.77053	2.300	0.410
Exposure, number of surgeries				
Natural direct effect	0.002	−0.01424	0.010	0.490
Natural indirect effect	0.003	−0.00286	0.010	0.210
Total effect	0.005	−0.01315	0.020	0.300
Proportion mediated	33.0%	−2.1715	2.710	0.300

CI = confidence interval; RACHS-1 = Risk Adjustment in Congenital Heart Surgery 1.

Mediation analysis

The results of the mediation analysis are shown in Table 3. The direct and indirect effects on epilepsy via perioperative clinical seizure were not statistically significant in any of the anatomical CHD classifications, Risk Adjustment in Congenital Heart Surgery 1, and number of surgeries. The proportion mediated for anatomical CHD classification, Risk Adjustment in Congenital Heart Surgery 1, and the number of surgeries was 22.0, 21.0, and 33.0%, respectively.

Imaging characteristics of patients with epilepsy

Brain imaging tests were performed in 20 of 23 patients with perioperative clinical seizure and all 15 patients with epilepsy. Table 4 shows the clinical features of the perioperative clinical seizure and/or epilepsy groups. Notable imaging findings were observed in 16 of 20 patients (80.0%) with perioperative clinical seizure; of those, 10 (62.5%) were subsequently diagnosed with epilepsy. Notable imaging findings were observed in 13 of 15 patients (86.7%) with epilepsy: eight patients with cerebral infarction; three patients with hypoxic-ischaemic encephalopathy; and two patients with cerebral haemorrhage. In the 15 patients with epilepsy, the imaging analysis did not reveal white matter integrity. Partial seizures were observed in 10 of 15 patients (66.7%), while generalised seizures were observed in five of 15 patients (33.3%).

Discussion

In the present study, the incidence of perioperative clinical seizure and epilepsy was 3.0 and 1.9%, respectively. These rates were slightly lower than those previously reported.

Currently, there is no consensus on the risk factors for epilepsy in post-operative patients with CHD. A prospective cohort study using univariate logistic regression analysis in 128 post-operative patients with CHD demonstrated that post-operative use of extracorporeal membrane oxygenation and longer hospital stay were risk factors for epilepsy.[14] A population-based cohort study involving 15,222 patients with CHD reported that the risk of epilepsy was most elevated among those who underwent multiple surgeries.[5]

In this study, we found that anatomical CHD classification, Risk Adjustment in Congenital Heart Surgery 1, and the number of surgeries were risk factors for developing epilepsy. Although brain injury is thought to be associated with the development of epilepsy, the mechanism of brain damage during the CHD perioperative period involves multiple factors. The exact mechanism responsible for brain injury in CHD is not yet fully understood, and several theories have been developed. Firstly, brain development could differ in infants with CHD because of intrinsic (epi)genetic factors. A large part of heart and brain development occurs simultaneously in the human fetus and involves shared genetic pathways. A discrepancy in one of these genetic pathways may lead to abnormal development of both organs, thereby causing neurodevelopmental

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Table 4. Imaging characteristics of patients with perioperative clinical seizure and/or epilepsy

Perioperative clinical seizure	Epilepsy	Brain imaging	Patterns of brain injury	Type of CHD	Cerebral infarction vascular territories or patterns of acquired brain injuries	Type of seizure
+	+	CT, MRI	Cerebral infarction	Polysplenia, SRV	Left MCA	Partial
+	+	CT	Cerebral infarction	MS	Left MCA	Generalised
+	+	CT, MRI	Cerebral infarction	PA/IVS	Left MCA	Partial
+	+	CT	Cerebral infarction	Ebstein's anomaly	Left MCA	Partial
+	+	CT, MRI	Cerebral infarction	TGA	Left MCA	Generalised
+	+	CT, MRI	Cerebral infarction	PA/VSD	Right PCA	Partial
+	+	MRI	Cerebral infarction	DILV, SLV	Left MCA	Partial
+	+	MRI	Cerebral infarction	AVSD, SRV	Right MCA	Partial
+	+	CT, MRI	HIE	HLHS	Total brain injury	Partial
+	+	CT	HIE	Asplenia, SRV	Total brain injury	Partial
–	+	CT, MRI	HIE	Severe MR	Total brain injury	Generalised
–	+	MRI	Cerebral haemorrhage	Polysplenia, SRV	Total brain injury	Generalised
–	+	MRI	Cerebral haemorrhage	HLHS	Multiple small infarcts	Partial
–	+	CT	None	Ebstein's anomaly	No brain injury	Partial
–	+	MRI	None	PA/IVS, Ebstein's anomaly	No brain injury	Generalised
+	–	MRI	Cerebral haemorrhage	CoA	Total brain injury	Partial
+	–	MRI	Cerebral infarction	PA/VSD	Multiple small infarcts	Generalised
+	–	MRI	Cerebral infarction	DAA	border zone infarct	Partial
+	–	CT, MRI	Cerebral infarction	DILV, SLV	Right MCA, right PCA	Partial
+	–	CT, MRI	Cerebral infarction	SRV, TAPVD	Left ACA	Partial
+	–	CT, MRI	Cerebral infarction	HLHS	Left MCA	Partial
+	–	CT, MRI	None	VSD	No brain injury	Generalised
+	–	CT	None	SRV	No brain injury	Partial
+	–	CT	None	AVSD	No brain injury	Generalised
+	–	CT, MRI	None	VSD	No brain injury	Generalised
+	–	No imaging	No imaging	VSD	No imaging	Generalised
+	–	No imaging	No imaging	VSD, ASD	No imaging	Generalised
+	–	No imaging	No imaging	AVSD	No imaging	Partial

ACA = anterior cerebral artery; AVSD = atrioventricular septal defect; CoA = coarctation of aorta; DAA = double aortic arch; DILV = double inlet left ventricle; HIE = hypoxic-ischaemic encephalopathy; HLHS = hypoplastic left heart syndrome; MCA = middle cerebral artery; MR = mitral valve regurgitation; MS = mitral valve stenosis; PA/IVS = pulmonary atresia with intact ventricular septum; PA/VSD = pulmonary atresia with ventricular septal defect; PCA = posterior cerebral artery; PCS = perioperative clinical seizures; SLV = single left ventricle; SRV = single right ventricle; TAPVD = total anomalous pulmonary venous drainage; TGA = transposition of the great arteries; VSD = ventricular septum defect.

impairments.[15] Secondly, the heart defect may entail changes in oxygen saturation because of intracardiac or extracardiac mixing. This may subsequently lead to circulatory alterations that affect oxygen and nutrient supply to the brain, thereby disrupting normal cerebral development.[15] Thirdly, decreased cerebral blood flow based on the specific sub-type of CHD is more pronounced in the presence of severe brain injury. For example, in conditions with left outflow tract obstruction (e.g. hypoplastic left heart syndrome, aortic valve stenosis), cerebral blood flow is supplied retrograde through the distal and transverse aortic arch by the ductus arteriosus. As pulmonary vascular resistance decreases, there is a potential for systemic steal to the pulmonary circulation. This is because adaptations to maintain systemic perfusion may be inadequate in the setting of single-ventricle physiology.[16] Fourthly, cardiopulmonary bypass operations to ensure intraoperative vital organ perfusion and oxygen supply are linked to specific risks (e.g. embolisation, deep hypothermia, flow rate, hemodilution, blood gas management, post-operative hyperthermia, systemic inflammatory response, and capillary leak syndrome). These may be risk factors for brain injury in patients with CHD during the perioperative period.[17] The anatomical complexity of CHD, high-risk cardiac surgery, and multiple cardiac surgeries that we have identified

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cause brain damage through various mechanisms, including the above.

In contrast to previous reports, the use or lack of post-operative extracorporeal membrane oxygenation was not identified as a risk factor. The present study showed that patients who used extracorporeal membrane oxygenation for a long time had more severe conditions and were at a higher risk of death. Therefore, even if the use of post-operative extracorporeal membrane oxygenation causes brain damage and epilepsy, it was not possible to retrospectively determine the development of epilepsy due to the large number of deaths. The analysis performed using the elastic net method may have been unable to recognise the use or lack of post-operative extracorporeal membrane oxygenation as a risk factor.

In this study, mediation analysis was performed to determine the involvement of perioperative clinical seizure in the development of epilepsy. The results showed that the anatomical complexity of CHD, high-risk cardiac surgery, and multiple cardiac surgeries had limited indirect involvement via perioperative clinical seizures. A perioperative clinical seizure may be the first symptom of epilepsy and clinically involved in its development. However, epilepsy may occur even in the absence of perioperative clinical seizure after surgery for CHD. Patients with high-risk factors may develop epilepsy with or without perioperative clinical seizure and require long-term monitoring.

The elastic net method identified anatomical CHD classification, Risk Adjustment in Congenital Heart Surgery 1, and the number of surgeries as potential risk factors for developing epilepsy; however, there was no significant difference found in the mediation analysis. This may be attributed to the small number of events; thus, more cases should be accumulated and analysed.

In this study, 10 of the 15 patients with epilepsy experienced stroke (cerebral infarction and cerebral haemorrhage), and three patients had hypoxic-ischaemic encephalopathy but no white matter integrity. White matter integrity has been observed at a high rate before and after surgery in newborn babies with CHD.[18] Of the four patients who developed epilepsy after surgery for CHD, three had hypoxic-ischaemic encephalopathy and one had no findings. Hence, it was concluded that white matter integrity was not associated with the development of epilepsy.[14] Brain imaging tests were not systematically performed, and it was not possible to evaluate the timing of brain damage occurrence. Moreover, the factors responsible for the occurrence of brain damage remain unknown. It has been reported that 16% of patients after CHD surgery with cardiopulmonary bypass had new white matter integrity.[19] Despite the high incidence of white matter integrity in post-operative patients with CHD, its absence in patients with epilepsy indicates that white matter integrity may not be involved in the development of this condition. Nevertheless, a high proportion (86.7%) of patients with epilepsy had stroke and hypoxic-ischaemic encephalopathy, indicating that these conditions may influence the development of epilepsy. In our study, partial and generalised seizures were observed in 10 (66.7%) and five (33.3%) of 15 patients, respectively. Since most incidents of stroke were associated with damage (also to the local grey matter), it is possible that numerous partial epilepsies occur, as observed in this study. The present study revealed that clinical features and imaging findings were in agreement.

There are some limitations in this study. Firstly, due to the retrospective nature of the study, electroencephalographic monitoring was not systematically performed after surgery for CHD. It is possible that some patients who had abnormalities detected through electroencephalography did not have clinical seizures. Therefore, the number of patients with perioperative clinical seizure may have been underestimated. Secondly, this study examined the development of epilepsy during an observation period of 4–7 years following surgery for CHD. Studies are warranted to determine the incidence of epilepsy after the aforementioned observation period. Thirdly, there was no significant difference found in the mediation analysis. Therefore, it is unclear whether the identified items are risk factors for developing epilepsy. This may be due to the low incidence of perioperative clinical seizure and epilepsy. Therefore, analysis of additional cases is warranted to obtain more accurate results. However, consistent with the clinical impression, anatomical CHD classification, Risk Adjustment in Congenital Heart Surgery 1, and the number of surgeries identified using the elastic net method were shown to cause epilepsy. Fourthly, brain imaging was not systematically performed on patients following CHD. Therefore, this study could not compare patients with and without perioperative clinical seizure and/or epilepsy. There may be patients who do not develop perioperative clinical seizure and/or epilepsy despite the presence of brain damage. Moreover, the threshold of brain damage that would cause perioperative clinical seizure and/or epilepsy remains unclear and should be determined in the future. Finally, brain MRI was not systematically performed. Therefore, six patients with epilepsy underwent brain CT only. Although white matter integrity can be detected non-invasively through MRI,[20] this approach is less sensitive than CT. This may explain the absence of white matter integrity in patients with epilepsy, as shown by brain imaging.

In summary, the incidence of perioperative clinical seizure and epilepsy was 3.0 and 1.9%, respectively. The anatomical complexity of CHD, high-risk cardiac surgery, and multiple cardiac surgeries were identified as potential risk factors for developing epilepsy, with a low rate of indirect involvement via perioperative clinical seizure and a high rate of direct involvement independently of perioperative clinical seizure. Unlike white matter integrity, stroke and hypoxic-ischaemic encephalopathy may also be linked to the development of epilepsy.

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Conflicts of interest. None.

Ethical standards. The authors assert that all procedures contributing to this work comply with the ethical standards of the relevant national guidelines on human experimentation (Ethical Guidelines for Medical and Health Research involving Human Subjects) and with the Helsinki Declaration of 1975, as revised in 2008, and has been approved by the Research Ethics Committee of Kanagawa Children's Medical Center (approval number: 1906-12).

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