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Research Article

Seizure Disorders in Pediatric Patients with Congenital Heart Disease

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Abstract

Introduction: An association between congenital heart disease (CHD) and seizures has been documented previously, with studies demonstrating up to 20% of children with CHD having seizures. Only a few studies have investigated this association and there is a paucity of data regarding what specific lesions, surgeries, and comorbidities may increase the risk of seizures. We used data from the Kids Inpatient Database (KIDS) to help characterize seizures in CHD and to investigate if there are independently associated findings.

Methods: Children with congenital heart disease were identified in the KIDS database from 1997 to 2012. Next, the presence or absence of seizures in these children was determined using ICD-9 coding. Univariate analyses were conducted to compare those with and without seizures. Next, regression analyses were conducted to determine what factors were independently associated with seizures in those with CHD. Finally, regression analyses were conducted to determine the impact of seizures on length, cost, and mortality of inpatient hospitalizations.

Results: A total of 361,476 inpatient admissions with congenital heart disease were identified. Of these, 2,927 (0.8%) had a documented seizure disorder. Older age was associated with increased risk of seizure disorder. Comorbidities associated with an increased likelihood of seizure disorder included respiratory failure and the presence of a genetic syndrome. Those with double outlet right ventricle, tetralogy of Fallot, Ebstein anomaly, and hypoplastic left heart syndrome were also more likely to have a seizure. Those undergoing heart transplant were also more likely to have seizures. Seizures did not increase length of stay, cost of stay, or mortality.

Conclusion: Specific cardiac lesions, cardiac surgeries, and comorbidities to alter the risk of seizures in children with CHD. Understanding these associations may help in identifying patients at higher risk for seizures. This can help in counseling and early identification of seizures in CHD patients.

Keywords: *Seizure Disorders; Pediatric Patients; Congenital Heart Disease*

Introduction

Studies have demonstrated that infants undergoing surgery for palliation or repair of congenital heart disease are at increased risk for postoperative seizures, with up to 20% of children having seizures evident by electroencephalography [1-8]. A majority of these seizures are not clinically evident and are only detected by electroencephalography, likely due to the use of medications such as benzodiazepines.

Independent factors associated with increased risk of postoperative seizures in infants include the use of deep hypothermic circulatory arrest, increased circulatory arrest duration, the presence of an identified genetic anomaly/syndrome, aortic arch obstruction, and delayed sternal closure.

Postoperative seizures have been demonstrated to increase early mortality and to negative impact development in children who have undergone repair of congenital heart disease [1-3]. Animal studies have also demonstrated that seizures increase the risk of subsequent seizures occurring in the future, a phenomenon that has not been investigated in children with congenital heart disease. Indeed, the burden of, and risk factors associated with, recurrent seizures in children with congenital heart disease have not been thoroughly investigated.

Aim of the Study

The aim of this study was to use the Kids' Inpatient Database (KIDS) a national inpatient database to estimate the burden of recurrent seizures in pediatric patients with congenital heart disease to determine risk factors for recurrent seizures in children with congenital heart disease.

Methods

Institutional review board review approval was waived as this studied utilizes deidentified data from a national database. Consent was not obtained by the authors for this study as the data was derived from a national database. This cross-sectional study is in compliance with the Helsinki declaration.

Kids' Inpatient Sample

The Kids' Inpatient Database, made available by the Healthcare Cost Utilization Project (HCUP) by the Agency for Healthcare Research and Quality (AHRQ) is a large database designed to capture data from community, non-rehabilitation hospital admissions in the United States. Community hospitals are defined differently by the database when compared to the definition used by some healthcare providers. The definition used by the database is as follows: "All non-Federal, short-term, general, and other specialty hospitals". Freestanding and non-freestanding children's hospitals are both included as are teaching and non-teaching hospitals. Discharges of patients less than 20 years of age are included in the database. Rehabilitation and long-term acute care hospitals are excluded from this database. Patients from all regions of the United States with a variety of payer types are captured in this database. Data from a total of 44 states is captured.

Patient identification

Data regarding hospital admissions was obtained from 6 available iterations of the database, spanning from 1997 to 2012. Patients with congenital heart disease and under 18 years of age were included in the final analysis. The determination of congenital heart disease and cardiac surgery were made based using ICD-9 coding as delineated below. Primary and secondary diagnosis fields were used to collect this data.

Only patients under 18 years of age were included in this analysis.

Data identification and collection

Seizure disorders were identified using codes 345.00 through 345.91. This category included diagnoses in which children experienced recurrent clinical seizures. Thus, subclinical seizures, or solitary seizures were not captured in this analysis. How seizures were diagnosed in the study population is not captured by the database and such this cannot be delineated. It should also be noted that the timing of seizures is only known to be as during the admission for cardiac surgery, specific timing such as preoperatively or postoperatively is not captured by the database and thus cannot be delineated in this analysis.

Demographic information including, gender, and race were collected for each admission. Admission characteristics such as admission month, length of stay, and cost of stay were collected as well. Information regarding comorbid conditions was also collected. Overweight or obese patients were identified using 278.00, 278.01, and 278.02. Acute kidney injury was identified using 584.9. Heart failure was identified using 428.0 to 428.9.

Congenital heart disease was identified using several ICD-9 codes: double outlet right ventricle using 745.11, atrioventricular septal defect using 745.60, partial anomalous pulmonary venous connection using 747.42, total anomalous pulmonary venous connection using 747.41, transposition of the great arteries using 745.10, congenitally corrected transposition using 745.12, hypoplastic left heart syndrome using 746.7, atrial septal defect using 745.61, ventricular septal defect using 745.5, pulmonary atresia with ventricular septal defect using 746.01, tricuspid atresia using 746.1, Ebstein anomaly using 746.2, truncus arteriosus using 745.0, and coronary artery anomaly using 746.85. Arrhythmias were identified using codes 427.0 to 427.42 as well as 426.0 to 426.13. It was not possible to distinguish between those with absence of a spleen or multiple spleens due to the ICD-9 coding strategy.

Cardiac surgery was identified using the following codes: codes 35.10 through 35.14 for valvuloplasty with no valve replacement, 35.20 through 35.28 for valvuloplasty with replacement, codes 35.50 through 35.73 for septal defect repair (including atrioventricular septal defect repair), 35.81 for complete repair of tetralogy of Fallot, 35.82 for pulmonary venous repair, 35.83 for complete repair of common arterial trunk, 35.84 for arterial switch operation for transposition, 35.91 for atrial switch operation for transposition, 35.92 for right ventricle to pulmonary artery conduit, 39.22 for Blalock-Tausig shunt, and 37.51 for heart transplant.

Statistical analysis

A cross-sectional study was conducted. Continuous variables are reported using median, minimum, and maximum, while categorical variables are reported using absolute frequency and percentages. Continuous variables were analyzed using a student t-test or Mann-Whitney-U test as appropriate with categorical variables being analyzed using chi-square analysis. Baseline characteristics, cardiac morphology, cardiac surgery, and other combordities were compared between those with and without a seizure disorder.

A logistic regression was then to determine factors associated with a seizure disorder with seizure disorder as the dependent variable. Next, logistic regression analysis was conducted to determine whether having a seizure disorder increased length of hospitalization, cost of hospitalization, or inpatient mortality. While these served as dependent variables in separate regression analyses, the independent variables included seizure disorder. Cost of stay used represents the total charges recorded for the admission.

All statistical analysis was done utilizing SPSS Version 20.0 (Chicago, IL).

Results

Characteristics of those with and without a seizure disorder

A total of 361,476 patients with congenital heart disease were included in the final analysis. Of these, 2,927 (0.8%) patients had a seizure disorder. Admissions with a seizure disorder tended to be older with a median of 2 years of age compared to a median of 0.1 years in those without a seizure disorder ($p < 0.001$). Those with a seizure disorder were more likely to be Caucasian or Native American when compared to those without a seizure disorder ($p < 0.001$). Respiratory failure was more likely in those with seizure disorder (odds ratio 3.2, 95% confidence interval 2.7 to 3.7, $p < 0.001$). Heart failure, acute kidney injury, and liver failure did not differ between the two groups. No significant difference in tachyarrhythmias or atrioventricular block was found between the two groups. Those with a seizure disorder were also more likely to have a syndrome when compared to those without a seizure disorder (OR 2.0, 95%CI 1.8 to 2.2, $p < 0.001$). There was no difference in the presence of isomerism, or so-called heterotaxy, between those with and without seizures (Table 1).

In regards to cardiac lesions, those with seizure disorders were more likely to have double outlet right ventricle (OR 1.3, 95%CI 1.1 to 1.6, $p < 0.001$), tetralogy of Fallot (OR 1.2, 95%CI 1.1 to 1.3, $p = 0.004$), Ebstein anomaly (OR 2.0, 95%CI 1.5 to 2.7, $p < 0.001$), and hypoplastic left heart syndrome (OR 2.2, 95%CI 2.0 to 2.5) (Table 1).

In regards to cardiac surgery, those with seizure disorders were more likely to have undergone heart transplant (OR 4.5, 95%CI 2.3 to 8.9) (Table 1).

Length of stay was shorter in those with a seizure disorder (median of 4 days versus a median of 5 days, $p< 0.001$) as was inpatient mortality (OR 0.7 95%CI 0.5 to 0.9, $p= 0.028$). Cost of hospitalization did not significantly differ between the two groups (Table 1).

	No seizure (n = 358,549)	Seizure (n=2,927)	Odds ratio (95% confidence interval)	p-value
Age (years)	0.1 (0 to 17)	2 (0 to 17)	--	< 0.001
Race			--	< 0.001
White	143,981 (48.4)	1,397 (54.6)		
Black	45,427 (15.3)	326 (12.7)		
Hispanic	75,694 (25.4)	579 (22.6)		
Asian or Pacific Islander	10,924 (3.7)	72 (2.8)		
Native American	2,393 (0.8)	31 (1.2)		
Other	19,290 (6.5)	152 (5.9)		
Heart failure	24,055 (6.7)	191 (6.5)	0.9 (0.8 to 1.1)	0.695
Respiratory failure	7,481 (2.1)	188 (6.4)	3.2 (2.7 to 3.7)	< 0.001
Acute kidney injury	4,285 (1.2)	40 (1.4)	1.1 (0.8 to 1.5)	0.395
Liver failure	596 (0.2)	***	0.8 (0.3 to 2.1)	0.696
Arrhythmia (not including atrioventricular block)	2,777 (0.8)	22 (0.8)	0.9 (0.6 to 1.4)	0.889
Atrioventricular block	1,769 (0.5)	21 (0.7)	1.4 (0.9 to 2.2)	0.085
Syndrome	32,017 (8.9)	486 (16.6)	2.0 (1.8 to 2.2)	< 0.001
Isomerism (heterotaxy)	4,304 (1.2)	36 (1.2)	1.0 (0.7 to 1.4)	0.883
Cardiac lesion				
Double outlet right ventricle	10,499 (2.9)	115 (3.9)	1.3 (1.1 to 1.6)	0.001
Atrioventricular septal defect	16,573 (4.6)	112 (3.8)	0.8 (0.6 to 0.9)	0.041
Partial anomalous pulmonary venous	2,174 (0.6)	18 (0.6)	1.0 (0.6 to 1.6)	0.952
connection	3,875 (1.1)	24 (0.8)	0.7 (0.5 to 1.1)	0.174
Total anomalous pulmonary venous connection	3,936 (1.1)	30 (1.0)	0.9 (0.6 to 1.3)	0.707
Coronary artery anomaly	217,395 (60.6)	1,562 (53.4)	0.7 (0.6 to 0.8)	< 0.001
Atrial septal defect	23,343 (6.5)	229 (7.8)	1.2 (1.1 to 1.3)	0.004
Tetralogy of Fallot	119,100 (33.2)	835 (28.5)	0.8 (0.7 to 0.8)	< 0.001
Ventricular septal defect	5,626 (1.6)}	28 (1.0)	0.6 (0.4 to 0.8)	0.008
Pulmonary atresia	6,528 (1.8)	50 (1.7)	0.9 (0.7 to 1.2)	0.651
Tricuspid atresia	3,185 (0.9)	53 (1.8)	2.0 (1.5 to 2.7)	< 0.001
Ebstein anomaly	15,290 (4.3)	271 (9.3)	2.2 (2.0 to 2.5)	< 0.001
Hypoplastic left heart syndrome	6,478 (1.8)	29 (1.0)	0.5 (0.3 to 0.7)	0.001
Transposition	1,918 (0.5)	14 (0.5)	0.8 (0.5 to 1.5)	0.676
Congenitally corrected transposition	3,445 (1.0)	31 (1.1)	1.1 (0.7 to 1.5)	0.587
Common arterial trunk				
Cardiac surgery				
Valvuloplasty, no valve replacement	5,701 (2.1)	29 (1.5)		0.053
Valvuloplasty with valve replacement	2,242 (0.8)	16 (0.8)	0.6 (0.4 to 1.0)	0.950
Septal defect repair	33,941 (12.6)	141 (7.2)	0.9 (0.6 to 1.6)	< 0.001
Tetralogy of Fallot, complete repair	5,737 (2.1)	28 (1.4)	0.5 (0.4 to 0.6)	0.034
Common arterial trunk, complete repair	815 (0.3)	***	0.6 (0.4 to 0.9)	0.108
Total anomalous pulmonary venous connection	2,205 (0.8)	4 (0.2)	0.3 (0.1 to 1.3)	0.003
repair	2,719 (1.0)	***	0.2 (0.1 to 0.6)	< 0.001
Transposition repair, arterial switch	904 (0.3)	***	--	0.545
Transposition, atrial switch	3,122 (1.2)	21 (1.1)	0.7 (0.3 to 1.8)	0.731
Right ventricle to pulmonary artery conduit	48 (0.1)	***	0.9 (0.6 to 1.4)	0.555
Blalock-Tausig shunt	4,599 (1.7)	35 (1.8)	--	0.772
Glenn	3,988 (1.5)	25 (1.3)	1.0 (0.7 to 1.4)	0.466
Fontan	271 (0.1)	***	0.8 (0.5 to 1.2)	< 0.001
Heart transplant			4.5 (2.3 to 8.9)	
Length of hospital stay (days)	5 (0 to 876)	4 (0 to 320)	--	< 0.001
Cost of hospitalization (US dollars)	28,376	29,447	--	0.191
Inpatient mortality	9,866 (2.8)	61 (2.1)	0.7 (0.5 to 0.9)	0.028

Table 1: *Characteristics of those with congenital heart disease, with and without a seizure disorder.*

**** Represents an absolute frequency less than 10 which per database policies cannot be explicitly reported.*

Independent risk factors associated with seizure disorders

Multivariate logistic regression with seizure disorder as the dependent variable demonstrated the following to be significantly associated with increased risk for a seizure disorder: age in years (OR 1.1, 95%CI 1.1 to 1.1), obstructive sleep apnea (OR 5.7, 95%CI 4.4 to 7.4), hypertension (OR 1.8, 95%CI 1.4 to 2.4), double outlet right ventricle (OR 1.3, 95%CI 1.1 to 1.7), hypoplastic left heart syndrome (OR 1.7, 95%CI 1.4 to 2.1), respiratory failure (OR 3.2, 95%CI 2.7 to 3.9), and presence of a syndrome (OR 2.0, 95%CI 1.7 to 2.3) (Table 2).

Factors associated with increased risk of seizures in those with congenital heart disease Odds ratio (95% Confidence interval)	
➢ Age (years)- 1.1 (1.1 to 1.1)	➢ Obstructive sleep apnea- 5.7 (4.4 to 7.4)
➢ Hypertension- 1.8 (1.4 to 2.4)	➢ Double outlet right ventricle- 1.3 (1.1 to 1.7)
➢ Hypoplastic left heart syndrome- 1.7 (1.4 to 2.1)	➢ Respiratory failure 3.2 (2.7 to 3.9)
➢ Syndrome- 2.0 (1.7 to 2.3)	

Table 2: *Factors independently associated with seizure disorders in those with congenital heart diseases.*

Impact of seizure disorders on inpatient admissions

When multivariate linear regression was done to determine the impact of seizure disorder on length of stay and cost of stay for inpatient hospitalizations, the presence of a seizure disorder significantly decreased length of stay by 2.5 days ($p < 0.001$). There was no significant difference in total charges for the hospitalization. Multivariate logistic regression was done to determine the impact of seizure disorder on inpatient mortality and demonstrated no significant difference in inpatient mortality associated with a seizure disorder (Table 3).

Outcome	Odds ratio with 95% confidence interval or beta-coefficient	p-value
Inpatient mortality	0.7 (0.5 to 1.0)	0.113
Length of stay	-2.5	< 0.001
Total charges	$8,213	0.141

Table 3: *Impact of seizure disorders on inpatient hospitalization characteristics.*

Discussion

Data from the Kids' Inpatient Database demonstrates that at least 0.8% of children with congenital heart disease will have recurrent seizures. Increasing age, obstructive sleep apnea, hypertension, double outlet right ventricle, hypoplastic left heart syndrome, respiratory failure, and the presence of a syndrome were identified to be independent risk factors associated with recurrent seizures. Children with any of these risk factors may benefit from formal monitoring for seizures for 24 hours postoperatively. Additional studies beyond ours will be needed to truly determine the period of such monitoring as our current study was not able to capture timing of seizures during in relation to cardiac surgery. Such monitoring may be important as previous studies have demonstrated impaired neurodevelopment in those with seizures during admissions for cardiac surgery.

In our study, multivariate regression analysis demonstrated that presence of a seizure disorder did not impact inpatient mortality or total charges. Interestingly, there was a decrease in the length of stay by 2.5 days. It is unclear what the mechanism of this is as additional data is not available to help investigate this further.

Previous data on recurrent seizures in those with congenital heart disease is not available although a handful of studies has investigated postoperative seizures. These studies have found that up to 20% of undergoing congenital heart surgery will experience postoperative seizures. Data from these studies is summarized in table 4 [1-8].

Study	Patient number	Patient population	Postoperative EEG duration	EEG seizures	Clinical seizures	Independent risk factors associated with seizures (multivariate analysis)	Impact of seizures on mortality and development
Newburger (1993)	171 (Only 136 w/EEG)	Infant arterial switch	48 hours	27 (20%)	11 (6%)	DHCA, presence of ventricular septal defect, preoperative acidosis	--
Clancy (2003)	164	Infant FUV and BV repairs	(Only clinical monitoring up to 6 weeks or discharge)	--	29 (18%)	Genetic condition, aortic arch obstruction, DHCA over 60 minutes	
Clancy (2005)	183	FUV and BV repairs prior to 6 months of age	48 hours	21 (12%)	--	--	--
Gaynor (2005)	178	FUV and BV repairs prior to 6 months of age	48 hours	20 (11%)	--	Increasing DHCA duration	--
Andropoulos (2010)	68	FUV and BV repairs prior to 30 days of age	72 hours	1 (2%)	0	--	--
Gunn (2012)	150	FUV and BV repairs prior to 2 months of age	72 hours	27 (19%)	0	--	Increased mortality, worsened neurodevelopment
Gunn (2012)	39	Functionally univentricular repairs prior to 30 days of age	72 hours	7 (18%)	--	--	Increased mortality, worsened development
Naim (2015)	161	FUV and BV repairs prior to 30 days of age	48 hours (or 24 hours after last seizure)	13 (8%)	11 (7%)	Delayed sternal closure, increasing DHCA duration	Increased mortality

Table 4: *Summary of previously published data on postoperative seizures in those with congenital heart disease.*
EEG: Electroencephalography; FUV: Functionally Univentricular; BV: Biventricular; DHCA: Deep Hypothermic Circulatory Arrest.

These studies noted that most postoperative seizures were noted only by electroencephalography and had no clinical correlate and were more likely in those who had surgery done with the use of deep hypothermic circulatory arrest. While several studies excluded children with identified syndromes, the ones that did not did identify this as a risk factor for postoperative seizures as well.

Our study, investigated burden and risk factors of recurrent seizures compared to the previous studies which looked at seizures in the first 72 hours, postoperatively. Thus, the risk factors our current study has identified do differ.

It is logical to expect the risk of recurrent seizures to increase with age since recurrence is more likely over a larger period of time. Our study demonstrates a 10% increase in the odds of recurrent seizures with every additional year of age.

Our study also identified that obstructive sleep apnea was associated with nearly 6-fold increase in the odds off a seizure disorder [9]. This has been previously described and is believed to be related to increase in non-REM sleep during which there is an increased risk of seizures, increased neuronal excitability, and hypoxia. Also of note is that those with seizures and obstructive sleep apnea tend to have worse cognitive function [10-13]. While these particular findings have been demonstrated in those without congenital heart disease, it is of particular interest in those with congenital heart disease since cognitive function may already be impaired in those with congenital heart disease and thus presence of a seizure disorder may further impact this [14,15].

The presence of a syndrome was identified to be associated with a 2-fold increase in the odds of a seizure disorder. This has been documented for particular syndromes in the past and is the result of syndrome-specific mechanisms. Although our study did not look at specific syndromes, it would seem logical that those with trisomy 13, trisomy 18, and DiGeorge syndrome would be at increased risk for seizure disorders due to the natural history of these syndromes.

While several cardiac diagnoses and surgeries were included in the multivariable analysis, only the diagnoses of double outlet right ventricle and hypoplastic left heart syndrome were associated with an increased risk of seizure disorder. Those with double outlet right ventricle had a 1.3-fold increase in the odds of a seizure disorder while those with hypoplastic left heart syndrome had a 1.7-fold increase in the odds of a seizure disorder. Those with hypoplastic left heart syndrome must undergo functionally univentricular palliation while some of those with double outlet right ventricle may also undergo functionally univentricular palliation. Previous studies have demonstrated that functionally univentricular palliation is associated with increased risk of postoperative seizures [3,6]. This has been thought to be secondary to the use of deep hypothermic circulatory arrest, particularly when duration of such circulatory arrest is greater than 40 minutes [5]. This is believed to lead to neuronal damage, particularly in watershed areas in the frontal and central areas which can then become foci for seizures. Additionally, preoperative hypoxia in children undergoing functionally univentricular palliation may lead to a decrease in the seizure threshold by causing neuronal damage and subsequently increasing neuronal excitability.

Double outlet right ventricle and hypoplastic left heart syndrome both can require long operative times and thus it is not particularly surprising that these two diagnoses are associated with increased risk for seizure disorder. Unfortunately, operative characteristics such as cardiopulmonary bypass time, use of deep hypothermic circulatory arrest, and duration of deep hypothermic circulatory arrest are not able to be captured from the KIDS database. While Stage I operations could not be identified specifically in this database, it is interesting to note that neither the Glenn or Fontan procedure which were specifically identified were not found to be independently associated with an increased risk of seizure disorder.

Additionally, one must consider that those with preoperative seizures may have suffered from such seizures due to focal brain abnormalities or due to hypoxia secondary to fetal hypoxia.

This study is not without its limitations. Not all ICD-9 codes have been validated over the years, particularly those used to code for congenital heart disease. Coding for complex congenital heart disease may be quite variable from provider to provider. Additionally, it must be kept in mind that the overall denominator is that of admissions and not individual patients. It is not possible with the database to identify unique patients and group admissions by patient.

This may lead to underestimation of the frequency of seizure disorder although the odds ratios should, however, should still provide an accurate depiction of the odds of seizure disorder compared between the two groups. Furthermore, data regarding operative characteristics such as cardiopulmonary bypass strategy, duration of cardiopulmonary bypass, use of deep hypothermic circulatory

arrest, and duration of deep hypothermic circulatory arrest could not be extracted from this database. How seizures were diagnosed, whether or not treatment was provided, and relation of seizures to the cardiac surgery were not captured in the database and thus could not be commented on in this study.

Conclusion

Seizure disorders are infrequent in children with congenital heart disease. Independent factors associated with increased risk of a seizure disorder include older age, obstructive sleep apnea, hypertension, double outlet right ventricle, hypoplastic left heart syndrome, and the presence of a genetic syndrome.

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