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Heart and Circulation

Research Article Open Access

Incidence of Brain and Renal Abnormalities in Newborns with Congenital Heart Disease: a Single Center Experience

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Received: 07 August 2017; **Accepted:** 29 August 2017; **Published: 05 September** 2017

Abstract

Objective: To define the incidence of brain and kidney anomalies in newborns with significant congenital heart disease admitted to the cardiac intensive care unit at Nicklaus Children's Hospital.

Study Design: A retrospective chart review of head and renal ultrasound was studied for newborns who were admitted with significant congenital heart disease to Nicklaus Children's Hospital cardiac intensive care unit from 2004 to 2010. As part of the institution protocol, genetic testing was also performed.

Result: A total of 548 patient charts were reviewed; of which, 19% (104) had clinically significant head ultrasound abnormalities, and 50.7% (278) had renal ultrasound abnormalities. Patients with septal defects were more likely to have clinically significant head ultrasound abnormalities (40.0%) than those with other types of congenital heart disease (17.8%; *P*=0.0025). Premature patients and those with genetic abnormalities were more likely to have clinically significant head ultrasound abnormalities than term patients (28.4% versus 17.0%, *P*=.01) or those without genetic abnormalities (25.3% versus 15.9%; *P*=.049). There was no increase in renal ultrasound abnormalities among those with genetic defects (54.7% versus 52.7, P= 0.75). Patients with dysmorphism had a higher risk of clinically significant head ultrasound (24.5%) and renal ultrasound abnormalities (59.5%) than non-dysmorphic patients (15.9%, *P*=.031; 47.1%, *P*=.008, respectively).

Conclusion: This study illustrates the high prevalence of renal and neurological abnormalities associated with congenital heart disease and confirms the utility of screening head and renal ultrasounds in newborns admitted with significant structural heart disease.

Keywords: Neonatal Screening; Congenital Malformations; Renal Ultrasound Abnormalities; Head Ultrasound Abnormalities

Introduction

The incidence of congenital heart disease (CHD) ranges from 6-8 per 1000 live births [1]. Almost all forms of complex CHD have some degree of palliation, which has shifted the outcome measure from decreasing mortality to minimizing morbidity. Despite the improved outcome, extracardiac abnormalities are common (22% to 45%) in this population, and studies have shown an increase in associated mortality [2]. The most frequent extracardiac abnormalities include craniofacial, genitourinary, neurological, and gastrointestinal abnormalities [2-4]. In addition, extracardiac abnormalities are associated with higher mortality, independent of the complexity of CHD [5].

Longitudinal studies suggest that some degree of neurodevelopmental impairment can be identified in approximately half of the survivors [6-8], which can be related to cardiopulmonary bypass at the time of the surgery or preoperative abnormalities as shown by brain MRI [9-11]. Research has also shown a relation between the embryological development of the brain and heart through neural crest cells, which is termed as cardiac neural crest. Studies have shown that ablation of these cells results in malformations including defective outflow tract septation (persistent truncus arteriosus), abnormal patterning of the aortic arch arteries and great arteries (such as interrupted aorta and double aortic arch), abnormal heart tube looping leading to arterial pole alignment defects (such as double outlet right ventricle), ventricular septal defects, and abnormal myocardial function resulting in decreased excitation-contraction (EC) coupling, contractility and L-type Ca^{+2} current [12].

Universal screening for genitourinary abnormalities in apparently normal children revealed an incidence of 0.96%, with varying degrees of clinical significance [13]. In contrast, increased incidence of anomalies of the kidney and urinary tract in patients with CHD ranged from 11.9% to 28% [3,14]. This incidence is high enough to advocate in favor of performing regular renal ultrasound (RUS) screening in patients with CHD. Studies have also proposed a genetic link between CHD and renal abnormalities that may be related to the conservation of development pathways and cell signal mechanisms [15].

Given this background, the aim of this study is to determine the incidence of abnormal head ultrasound (HUS) and RUS in all newborns with CHD admitted to the cardiac intensive care unit from 2004 to 2010.

Methods

The results of HUS and RUS, karyotyping and FISH studies, if available, were abstracted from the records of all newborns with CHD who were admitted to the Nicklaus Children's Hospital (NCH) cardiac intensive care unit (CICU) from January 1st, 2004 to December 31st, 2010 using a standardized abstraction form. The karyotyping and FISH results were reported in a previous study [16]. Patients' gestational age, sex, race and ethnicity, physical examination findings, and type and category of CHD were also obtained. The patients were examined by a clinician in the CICU for dysmorphic features, defined as any abnormally formed body structure (e.g. craniofacial abnormalities, webbed neck, skeletal and limb abnormalities). If dysmorphic features were identified the hospital geneticist was consulted. HUS abnormalities were further characterized as "clinically significant (CS)" based on their likelihood of being associated with neurodevelopmental abnormalities and need for follow-up. Cardiac abnormalities were grouped into 7 categories including conotruncal defects, right-sided obstructive defects, left-sided obstructive defects, single ventricle, septal defects, heterotaxy, and others.

Data were analyzed using Epi Info 3.5.3 for Windows (Centers for Disease Control and Prevention, 2011, Atlanta, GA). Prevalence of all HUS and CS-HUS abnormalities and RUS abnormalities were compared by demographics, physical examination of characteristics, CHD category, gestational age, and karyotype and FISH results. The strength of associations was assessed by hazard ratios as estimates of relative risk (RR); 95% confidence intervals (CIs) were used to assess the precision of estimates and significance testing. Chi-square and Fisher exact two-tailed p-values were also used for significance testing. To control for confounding, stratified analysis, and unconditional backward logistic regression was performed.

Results

From January 1, 2004 to December 31, 2010, 548 newborns had

HUS and RUS evaluations. Most of them (82.7%) were full-term newborns, and 55.8% were male (Table 1). The age at admission ranged from hours to 30 days. A majority of the infants were Hispanic (42.9%) and non-Hispanic White infants (34.9%), followed by African-American (18.6%) and other races (3.6%). About a third of the patients had conotruncal defects, 21.4% had left-sided obstructive lesions, and 19.7% had single ventricle defects. Overall, 29.7% (163 of 548) were dysmorphic, and 16.8% (75 of 447 with karyotype or FISH testing) had some genetic abnormality. Almost half of the patients (44.5%) had some form of HUS abnormality, but only 19% (104) of these were considered to be CS-HUS findings. Impressively, 50.7% (278) had RUS abnormalities. Additionally, 28.6% (157) patients had both normal head and renal ultrasound, however, 42.2% (231) had normal RUS and either a normal HUS or clinically insignificant HUS finding.

Table 1: Characteristics of newborns admitted with congenital heart disease (CHD) to the Miami Children's Hospital Cardiac Intensive Care Unit from 2004 to 2010.

Characteristic (N=548)	No (%)
Sex	
Female	242 (44.2)
Male	306 (55.8)
Race/Ethnicity	
Latino	235 (42.9)
White	191 (34.9)
African-American	102 (18.6)
Other	20 (3.6)
Gestational Age	
Premature	95 (17.3)
Term	453 (82.7)
Dysmorphism	
Dysmorphic	163 (29.7)
Non-Dysmorphic	385 (70.3)
Genetic Abnormalities*	
Any	75 (16.8)
None	372 (83.2)
Cardiac Defect Group	
Conotruncal Defects	182 (33.2)
Right Sided Obstructive Defects	49 (8.9)
Left Sided Obstructive Defects	117 (21.4)
Single Ventricle	108 (19.7)
Septal Defects	30 (5.5)
Heterotaxy	15 (2.7)
Other	47 (8.6)

*N=447

Compared to others, African-American and female patients were more likely to have HUS abnormality, but the prevalence of CS-HUS abnormalities did not differ significantly by gender, race or ethnicity (Table 2). In general, the risk of CS-HUS abnormalities did not vary significantly by cardiac abnormality, but patients with septal defects, which included atrioventricular (AV) canal and large ventricular septal defect (VSD), were over twice as likely to have CS-HUS abnormalities as patients with other types of CHD. Premature and dysmorphic newborns and those with genetic abnormalities detected by karyotype or FISH testing were more likely to have CS-HUS abnormalities than other newborns with CHD. The risk of RUS abnormalities did not vary by gender, race, ethnicity, or genetic abnormality (Table 3). Dysmorphic newborns and those who were premature were more likely to have abnormal RUS findings than others.

The risk of CS-HUS by prematurity, septal defects including AV canal and large VSD, and genetic abnormality did not differ when stratified by dysmorphism. In logistic regression when controlled for prematurity, genetic abnormalities, dysmorphism, and septal defects, prematurity and septal defects continued to be strongly and independently associated with clinically significant HUS abnormalities (Table 4a). Similarly, when controlled for prematurity and dysmorphism, dysmorphism remained independently associated with increased risk of RUS abnormalities (Table 4b).

In RUS pelvicalyceal dilation was the most common finding at 54%. This was followed by poor corticomedullary differentiation (12.2%) and echogenic kidney (10.1%) (Table 5). Among CS-HUS mineralizing angiopathy was the most common at 34.6% followed by periventricular white matter echogenicity (20.2%) and ventriculomegaly (8.7%) (Table 6).

Table 2: Characteristics associated with head ultrasound (HUS) and clinically significant head ultrasound (CS-HUS) findings.

Characteristic	**Number (%) with any HUS Finding**	**Total**	**Relative Risk (95%CI)**	***P***	**Number (%) with CS-HUS**	**Total**	**Relative Risk (95%CI)**	***P***
Sex								
Female	120 (49.6)	242	1.2	0.03	46 (19.0)	242	1.0	0.99
Male	124 (40.5)	306	(1.02-1.47)		58 (19.0)	306	(0.70-1.42)	
Race/Ethnicity				0.07				0.82
Latino	97 (41.3)	235			47 (20.0)	235		
White	80 (41.9)	191			34 (17.8)	191		
African-American	57 (55.9)	102			18 (17.6)	102		
Other	10 (50)	20			5 (25.0)	20		
Gestational Age								
Premature	49 (51.6)	95	0.92	.44	27 (28.4)	95	1.67	0.63
Term	255 (56.3)	453	(0.74-1.13)		77 (17.0)	453	(1.14-2.44)	
Dysmorphism								
Dysmorphic	88 (54.0)	163	1.33	.004	40 (24.5)	163	1.48	0.01
Non-Dysmorphic	156 (40.5)	385	(1.10-1.60)		64 (16.6)	385	(1.04-2.09)	
Genetic Abnormalities								
Any	42 (56)	75	1.31	0.031	19 (25.3)	75	1.60	0.03
None	160 (43.0)	372	(1.03-1.64)		59 (15.9)	372	(1.01-2.51)	
Septal Defect								
Any	18 (60.0)	30	1.38	0.079	12 (40.0)	30	2.25	0.049
None	226 (43.6)	518	(1.01-1.87)		92 (17.8)	518	(1.40-3.62)	
								0.003

Citation: Al-mousily MF, Dykes JC, Khan D, et al. Incidence of Brain and Renal Abnormalities in Newborns with Congenital Heart Disease: a Single Center Experience. Heart Circ 2017; 1:015.

Table 3: Characteristics associated with renal ultrasound (RUS) abnormalities.

Characteristic	Number (%) with RUS Abnormality	Total	Relative Risk (95%CI)	*P*
Sex				
Female	120 (49.6)	242	0.96	0.66
Male	158 (51.6)	306	(0.81-1.13)	
Race/Ethnicity				0.41
Latino	111 (47.2)	235		
White	106 (55.5)	191		
African-American	51 (50.0)	102		
Other	10 (50)	20		
Gestational Age				
Premature	56 (58.9)	95	1.20	0.08
Term	222 (49.0)	453	(0.99-1.46)	
Dysmorphism				
Dysmorphic	97 (59.5)	163	1.27	0.07
Non-Dysmorphic	181 (47.0)	385	(1.07-1.49)	
Genetic Abnormalities				
Any	41 (54.7)	75	1.04	0.75
None	196 (52.7)	372	(0.83-1.3)	

Table 4: Backward Unconditional Logistic regression analyses: characteristics independently associated with clinically significant head ultrasound (CS-HUS) findings (4a) and renal ultrasound (RUS) findings (4b) in newborns admitted with congenital heart disease to the Miami Children's Hospital Cardiac Intensive Care Unit, 2004 - 2010.

4a: Factors independently associated with clinically significant head ultrasound abnormalities, controlled for other factors.

Term	Odds Ratio	95%CI	Coefficient	S. E.	Z-Statistic	P-Value
Normal Genetics	0.79	0.41-1.54	-0.2383	0.3388	-0.7033	0.4819
Dysmorphic	1.36	0.77-2.40	0.3082	0.2909	1.0597	0.2893
Premature	1.83	1.01-3.30	0.6027	0.3013	2.0004	0.0455
Septal Defect	3.1	1.24-7.70	1.1291	0.4657	2.4247	0.0153
CONSTANT	*	*	-1.6842	0.3608	-4.6683	0

4b: Factors independently associated with abnormal renal ultrasound, controlled for other factors.

Term	Odds Ratio	(95%CI)	Coefficient	S. E.	P-Value
Dysmorphism	1.53	(1.05-2.23)	0.4256	0.1921	0.0268
Premature	1.42	(0.90-2.24)	0.3517	0.2323	0.13
CONSTANT	*	*	-0.0846	0.1128	0.4535

Table 5: Renal ultrasound (RUS) Abnormalities.

RUS Findings (N = 278)	Total (%)
Pelvicalyceal Dilation	150 (54.0)
Poor Corticomedullary Differentiation	34 (12.2)
Echogenic kidney	28 (10.1)
Hydronephrosis	17 (6.1)
Urothelial Thickening	10 (3.6)
Renal Parenchymal Cyst	9 (3.2)
Single Kidney	8 (2.9)
Small Kidney	7 (2.5)
Malrotated Kidney	5 (1.8)
Horseshoe Kidney	4 (1.4)
Duplex Collecting System	3 (1.1)
Ectopic Kidney	2 (0.7)
Multicystic Dysplastic kidney	1 (0.4)

Table 6: clinically significant head ultrasound (CS-HUS) Abnormalities.

CS-HUS Findings (N= 278)	Total (%)
Mineralizing Angiopathy	36 (34.6)
Periventricular White Matter Echogenicity	21 (20.2)
Ventriculomegaly	9 (8.7)
Corpus Callosal thinning or hypoplasia	8 (7.7)
IVH grade III/IV	7 (6.7)
Isolated Parenchymal Hemorrhage	4 (3.8)
Corpus Callosal Agenesis/Dysgenesis	4
Brain Edema	3 (2.9)
Dandy-Walker Syndrome	3
IVH Grade II	2 (1.9)
Calcification Thalamus and Basal Ganglia	1 (0.96)
Caudate hypoechoic	1
Vein of Galen Aneurysmal malformation	1
Holoprosencephaly	1
Subependymal Nodule	1
Chiari Type III	1
Brain Infarct	1

Discussion

A screening ultrasound is a quick, inexpensive, and minimally invasive method of detecting structural abnormalities which has been utilized in many patient populations. It is well known that children with CHD have a number of extracardiac abnormalities some which have immediate implications for cardiothoracic planning along with potential long-term prognostic implications. Extensive research has

been performed on the incidence of head and renal abnormalities in the CHD patient population [10,11,14]. We found a significantly increased percentage of abnormal RUS when compared to previous studies [3,14]. Our results showed that 19% of patients had CS-HUS and half of the patients had abnormal RUS findings on screening. Gender, race, and ethnicity were not found to be predictive of abnormal results on either CS-HUS or RUS screening. In addition, prematurity and those with septal defects including AV canal or large VSD have an increased risk of CS-HUS abnormality and that dysmorphism was associated with RUS abnormalities. In the early admission period, knowledge of these abnormalities may allow physicians to anticipate issues surrounding cardiac surgery and possibly intervene to decrease morbidity and mortality.

Among patients with CS-HUS abnormalities, 12.7% were found to have hemorrhagic findings including IVH grade II/III/IV and isolated parenchymal hemorrhage. Patients with hemorrhagic findings by HUS may alter the timing or degree of anticoagulation during cardiopulmonary bypass. Knowledge of even minor preoperative hemorrhagic findings can aid in the early detection of postoperative extension following cardiopulmonary bypass. It may also change the timing of surgery and may affect the decision to perform bypass versus non-bypass surgery. We also found a much higher rate of renal abnormalities than previously reported which is important given that cardiopulmonary bypass is a well-known inducer of acute kidney injury (AKI) [17]. Many patients also require cardiac catheterization, which may place them at risk for contrast-induced nephropathy (CIN). Certain structural findings on RUS may indicate an increase in risk for development of AKI or CIN and thus be important factors to consider in the risk-benefit analysis of perioperative diagnostic cardiac catheterization.

It is also important for the medical staff to be aware of these abnormalities to anticipate any complications that may arise and allow access to multidisciplinary care when appropriate. Once the patient is discharged from the hospital, knowledge of HUS and RUS findings may help practitioners anticipate further therapies that may benefit the patient and decrease cumulative morbidity over the child's lifetime. Previous studies have shown that newborns with CHD have a significant incidence of white matter injury that is associated with neurodevelopmental delay [18]. Findings noted early on HUS screening may help identify patients who are at increased risk of neurodevelopmental delay and ensure they have the proper follow-up after discharge. Early intervention, home therapy and neurodevelopmental clinics has been shown to improve outcomes in these patients, early identification by ultra sound should lead to better long- term outcomes.

Our single center study of newborns with significant heart disease revealed a significant incidence of brain and renal abnormalities that were found on screening ultrasound. Given the increased incidence of HUS and RUS abnormalities found in our study with the possibility of improved outcomes with early identification of these defects, we would advocate for early head and renal screening for patients with complex heart disease admitted to CICU. This aids the cardiac team to make decisions in reference to timing of procedures and surgery. Further research is required to investigate the utility of general screening for this patient population along with long-term outcome studies that might yield prognostic factors for increased morbidity.

Limitations

This study is a single center's experience, and Nicklaus Children's hospital is a tertiary center. As such, our patient population is biased towards patients requiring early intervention. Patients with minor CHD such as isolated atrial septal defect or small patent ductus arteriosus were not accounted for in our study, which may alter the true incidence of head and renal abnormalities. Our hospital underwent a transition to electronic medical records in 2012, which made data retrieval difficult for some patients in regards to genetic testing. Variability among radiologist readings and subjective threshold for reporting abnormal findings versus normal variants may alter the incidence of ultrasound abnormalities. Also, defining HUS and RUS findings as significant was a subjective process based on input from experts in the fields of neurology and nephrology, which has an inherent degree of clinical practice bias. There are also limited validated guidelines or clinical algorithms regarding the need for follow-up or advanced imaging for many of the HUS and RUS findings. There also exists an inherent limitation of ultrasound in detecting certain abnormalities such as minute white matter changes that may be better evaluated by MRI.

Author Contributions

A.M.F., D.J.C., and W.E. contributed to study design. A.M.F., D.J.C., A.E.D., D.D., and W.E. performed data acquisition. A.M.F. carried out data analysis. A.M.F., W.E., and K.D. performed literature review. A.M.F., D.J.C., D.D., and W.E. prepared the manuscript. All authors were involved in reviewing the manuscript.

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