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Critical Congenital Heart Disease – Utility of Routine Screening for Chromosomal and other Extracardiac Malformations

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Abstract

Objective—Infants with critical congenital heart disease (CHD) can have genetic and other extracardiac malformations, which add to the short and long term risk of morbidity and perhaps mortality. We sought to examine our center's practice of screening for extracardiac anomalies and to determine the yield of these tests among specific cardiac diagnostic categories.

Design—Retrospective review of infants admitted to the cardiac intensive care unit with a new diagnosis of CHD. Subjects were categorized into 6 groups: septal defects (SD), conotruncal defects (CTD), single-ventricle physiology (SV), left-sided obstructive lesions (LSO), right-sided obstructive lesions (RSO) and "other" (anomalous pulmonary venous return, Ebstein's anomaly). Screening modalities included genetic testing (karyotype and FISH for 22q11.2 deletion), renal ultrasound (RUS) and head ultrasound (HUS).

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Results—One hundred forty-one patients were identified. The incidence of cardiac anomalies was: CTD (36%), SD (18%), SV (18%), LSO (14%), RSO (3%) and “Other” (8%). Overall 14% had an abnormal karyotype, 5% had a deletion for 22q11.2, 28% had an abnormal RUS and 22% had abnormal HUS. Patients in SD and SV had the highest incidence of abnormal karyotype (36 and 17%); 22q11.2 deletion was present only in CTD and LSO groups (9 and 7% respectively); abnormal RUS and HUS were seen relatively uniformly in all categories. Premature infants had significantly higher incidence of renal 43 vs. 24%, and intracranial abnormalities 46 vs. 16%.

Conclusion—Infants with critical CHD and particularly premature infants, have a high incidence of genetic and other extracardiac anomalies. Universal screening for these abnormalities with ultrasonographic and genetic testing maybe warranted, since early detection could impact short and long term outcomes.

Keywords

Extracardiac Malformations; Renal Ultrasound; Head Ultrasound; Chromosomal Defects; Genetic Testing

Introduction

Extracardiac abnormalities in patients with critical congenital heart disease (CHD) can be associated with increased morbidity and mortality if not diagnosed early. The prevalence of CHD in live born infants is between 4-12 per 1000 (1-3). Twenty-two to 45% of patients with CHD have an associated chromosomal abnormality, genetic syndrome or extracardiac abnormality (1,2,4,5). Ultrasound and genetic testing are relatively easy and accurate methods to screen for important cerebral, renal and chromosomal abnormalities that may influence a patient's immediate or long term medical condition or surgical treatment course.

In this study, we sought to examine our center's practice of screening for extracardiac anomalies and to determine the yield of our screening tests among specific cardiac diagnostic categories.

Methods

This retrospective study was approved by the University of Pittsburgh Institutional Review Board and an informed consent to review the charts was waived. We reviewed the charts of all infants admitted to the cardiac intensive care unit (CICU) with a new diagnosis of CHD from 2004 to 2008. Data collected included age on admission, gestational age, gender, mortality and cardiac diagnosis. Information on extracardiac abnormalities included: genetic testing in the form of karyotype and fluorescent in situ hybridization (FISH) for 22q11.2 deletion; baseline and subsequent renal ultrasound (RUS) and head ultrasound (HUS) results; and preoperative and peak creatinine level during hospitalization.

Cardiac diagnoses were grouped into 6 mutually exclusive categories as previously described by Gonzalez et al (5). The categories were: septal defects (SD), conotruncal defects (CTD), functionally single-ventricle (SV) heart, left sided obstructive lesions (LSO), right sided obstructive lesions (RSO) and “other”. The SD group included patients with atrial septal defects, ventricular septal defects, and atrioventricular septal defects. The CTD group included patients with tetralogy of Fallot (TOF), TOF with pulmonary atresia, double outlet right ventricle, truncus arteriosus and transposition of the great arteries. The SV group included hypoplastic left heart syndrome, unbalanced atrioventricular canal with hypoplastic left or right ventricle, double inlet and double outlet single right ventricle and tricuspid atresia. The LSO group included patients with coarctation of the aorta, hypoplastic aortic arch, interrupted aortic arch (IAA), aortic valve stenosis and mitral valve stenosis. The RSO

group included patients with pulmonary atresia and pulmonary valve stenosis, and the “other” group contained patients with anomalous pulmonary venous return and Ebstein’s anomaly.

Statistical analysis

Data were entered into a data collection sheet and further analyzed using SPSS 16.0 software (SPSS Inc., Chicago, Illinois, United States of America). Data are presented as mean with standard deviation or median with interquartile range where appropriate. The Pearson Chi-Square test or the Fisher’s exact test was used to compare the results of each screening test between groups were appropriate. Analysis of continuous variables (gestational age and creatinine levels) was performed using a Mann-Whitney U test. All tests were two-sided and a p value of ≤ 0.05 was considered significant.

Results

The charts of 141 neonates and infants were reviewed. All except one of the patients in these series required surgical intervention. The baseline demographic information is shown in table 1.

Genetic Testing

One hundred nineteen patients (84%) had chromosomal analysis completed. Of those, 17 (14%) were abnormal (Table 2). The most common abnormality was trisomy 21 and was seen in 8 of the 17 patients (47%). Seven of these were among the SD group and 1 in the CTD group in a patient with TOF. The detail chromosomal abnormalities are shown in Table 3. Noteworthy that none of the patients in the CTD group and with the diagnosis transposition of the great arteries had an abnormal karyotype.

Genetic testing with FISH for 22q11.2 deletion by was done in 103 patients (73%), 5 of which had the deletion (5%) (Table 2). Four were detected in the CTD group, in patients with TOF and TOF with pulmonary atresia and 1 in the LSO group in a patient with IAA.

Renal abnormalities

There were 112 patients (79%) who had screening RUS performed on admission. Of those 31 (28%) were abnormal (Table 2). Pelviectasia, single kidney and nephrocalcinosis were the most common abnormalities seen (Table 4). Nineteen of the patients (61%) with abnormal baseline RUS had a follow-up study. The hydronephrosis, initially observed in 2 patients, resolved in 1 and improved in the other. From the patients with pelviectasia, 5 (23%) had normalized, 1 remained stable and 1 (8%) progressed to stage III vesicoureteral reflux. All 4 patients with nephrocalcinosis had normalized.

Preoperative and peak postoperative creatinine levels were compared in patients with normal and abnormal renal ultrasounds (Table 3). No significant differences were found, 0.54 ± 0.23 vs 0.53 ± 0.21 ($p = 0.13$) and 0.9 ± 0.42 vs 0.85 ± 0.37 ($p = 0.2$) respectively.

Cerebral abnormalities

A screening HUS was performed in 122 (86%) patients. Twenty-seven (22%) were abnormal (Table 2). Most common abnormality seen was Grade I IVH seen in 8 patients (7%) and increased extra-axial fluid seen in 6 (5%) (Table 5). Twenty-one of the 27 patients (78%) with abnormal initial HUS had a follow-up radiologic study (17 with HUS and 4 with CT or MRI scan). Of the 8 patients with Grade I IVH, 2 remain stable, 1 developed hydrocephalus, 1 cystic encephalomalacia, 1 changed to increased extra-axial fluid, 2 resolved, and 1 found to have dysplastic cerebellum on MRI.

Multiple Extracardiac Abnormalities

There were 9 patients who had more than one extracardiac abnormality (Table 6). Four of these patients belonged to the CTD group.

Gestational age

In these series there were 28 (20%) premature neonates (≤ 36 weeks gestational age). Among these there were 21 with available RUS studies, 9 of which were abnormal (43%). This is in contrast to the full-term infants where only 22 of the 91 available RUS were abnormal (24%) ($p = 0.09$).

Head ultrasounds were available for 26 (93%) of the premature neonates, 12 of which were abnormal (46%). This is again in contrast to the full-term infants where only 15 of the available 96 HUS were abnormal (16%) ($p = 0.001$).

Mortality

The infant mortality was 11% ($n=15$). Among the patients who died, there were 12 patients with genetic testing performed. All karyotypes were normal. The FISH test for 22q11.2 deletion was positive in 3 (25%). There were also 13 patients with RUS results, 4 of which were abnormal (31%). The preoperative creatinine level in those who survived was 0.46 ± 0.19 vs. 0.61 ± 0.32 in those who died ($p = 0.06$). The peak postoperative creatinine level was 0.72 ± 0.36 in survivors vs. 1.28 ± 0.57 in those who died ($p < 0.001$). All of the patients had a HUS done. Six of these were abnormal (40%) vs. 21 abnormal HUS (20%) in survivors ($p = 0.09$). The abnormal HUS included 2 with increased extra-axial fluid, 2 with absent corpus Callosum, 1 with Grade 1 IVH, and 1 with hydrocephalus. There was no difference in gestational age between survivors and non survivors ($p = 0.7$).

Discussion

The results from this cohort demonstrate that infants with critical CHD have associated extracardiac anomalies that warrant systematic diagnostic approach and follow-up. The overall incidence of having an abnormal karyotype and or deletion of 22q11.2 was 18%, an abnormal RUS 28%, and an abnormal HUS 22%. Among the aforementioned cardiac groups, the incidence of having at least one abnormality appeared to be similar in all groups ranging from 42 – 58% with the highest being in the SD and LSO groups (Table 2). This is similar to previous studies that showed that up to 45% of patients with CHD have extracardiac anomalies and that patients with septal defects and left-sided obstructive lesions tend to have more abnormalities than other types of CHD (2, 5).

Overall 14% of karyotypes and 5% of FISH 22q11.2 tests were abnormal. Most of the abnormal karyotypes were found in the SD and SV group of patients. These results are similar to the study done by Gonzales et al. in which patients with SD were 6.7 times more likely to have a genetic abnormality (5). Given the increased prevalence of neurodevelopmental delay in patients with critical CHD, the additional presence of any chromosomal abnormality could have an additive negative effect.

A substantial number of patients (28%) had renal abnormalities that were fairly uniform throughout the cardiac groups. This is different from the study by Gonzalez et al, where SD had a greater incidence of abnormalities (61%) (5). This may perhaps be attributed to the fact that the study by Gonzalez involved abdominal ultrasounds instead of only RUS and therefore able to detect other potential intra-abdominal pathologies. Though in our study the presence of renal abnormalities did not appear to have an effect on the creatinine level, these patients would still need a long term follow-up as some of these pathologies have the

potential to worsen and cause renal insufficiency. In addition some of these abnormalities would need empiric antibiotic prophylaxis and benefit from increased vigilance in they would to be given agents with potential for nephrotoxicity.

The incidence of any intracranial abnormality was 22% and the majority of these abnormalities were seen in the CTD and SD groups. Previous studies have reported ultrasonographic abnormalities between 20 and 50% (6, 7). Though HUS is a very fast and easily obtainable screening test it is not as sensitive as other modalities for the detection of subtle findings. This may explain the difference between our study and a study by Tavani et al. who reported a 62% incidence of intracranial hemorrhage detected by MRI (8). As with the presence of chromosomal abnormalities these patients would benefit from long term neurodevelopmental intervention and follow-up in addition to close monitoring during the immediate postoperative period. It is not clear what the implication of Grade I IVH or subdural hemorrhage is during the perioperative period and whether cardiopulmonary bypass associated heparin administration and surgery needs to be delayed. In our institution, when possible, we have traditionally delayed heparin administration and thus surgery for one week, after the lesion was declared “stable” by repeat imaging.

Another important result from this study is the significantly higher renal (43 vs. 24%) and intracranial (46 vs. 16%) abnormalities in premature vs. full-term infants. This increase incidence of extracardiac anomalies perhaps explains to an extent, the increase morbidity seen in this patient population after cardiac surgery.

Though mortality could not be attributed to any abnormal test, there was a trend toward increased mortality in patients with abnormal HUS ($p = 0.09$).

Limitations

Our study is limited by its retrospective nature. Not all patients had all 4 tests performed and in some patients data could not be found. During our screening procedure we excluded patients who did not have any of the 4 aforementioned exams performed. This creates a bias and overestimates the actual incidence of extracardiac anomalies and perhaps mortality in our patient population. We did not collect any dysmorphology data as much of the information available in medical records was insufficient. Additionally it is possible that the number of patients with 22q11.2 deletion is underestimated due to testing by FISH and not by the more sensitive microarray analysis.

Conclusion

The current study provides evidence that infants and particularly premature infants with critical CHD have an increased incidence of extracardiac anomalies. The majority of these abnormalities can be detected with routine, brief ultrasonographic and genetic testing. Though the presence of any of these anomalies may or may not have a direct impact on the initial perioperative period, knowledge of these multisystem abnormalities is important for the caring physician to employ appropriate early neurodevelopmental intervention and prevention of organ dysfunction. Extracardiac abnormalities warrant regular monitoring to take timely preventative measures and improve management.

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References

1. Tennstedt C, Chaoui R, Korner H, Dietel M. Spectrum of congenital heart defects and extracardiac malformations associated with chromosomal abnormalities: results of a seven year necropsy study. *Heart*. 1999; 82:34–39. [PubMed: 10377306]
2. Gucer S, Tolga I, Kale G, Akcoren Z, Ozkutlu S, Talim B, Caqlar M. Noncardiac malformations in congenital heart disease: A retrospective analysis of 305 pediatric autopsies. *Turk J Pediatr*. 2005; 47:159–166. [PubMed: 16052857]
3. Grech V, Gatt M. Syndromes and malformations associated with congenital heart disease in a population-based study. *Int J Cardiol*. 1999; 68:151–156. [PubMed: 10189002]
4. Meberg A, Hals J, Thaulow E. Congenital heart defects-chromosomal anomalies, syndromes and extracardiac malformation. *Acta Paediatrica*. 2007; 96:1142–1145. [PubMed: 17590185]
5. Gonzales J, Shirali G, Atz A, Taylor SN, Forbus GA, Zyblewski SC, Hlavacek AM. Universal Screening for Extracardiac Abnormalities in Neonates with Congenital heart disease. *Pediatr Cardiol*. 2009; 30:269–273. [PubMed: 19082649]
6. Te Pas A, Van Wezel-Meijler G, Bokenkamp-Gramann R. *Acta Paediatrica*. 2005; 94:1597–1603. [PubMed: 16352496]
7. van Houten JP, Rothman A, Bejar R. High incidence of cranial ultrasound abnormalities in full-term infants with congenital heart disease. *Am J Perinatol*. 1996; 13:47–53. [PubMed: 8645386]
8. Tavani F, Zimmerman RA, Clancy RR, Licht DJ, Mahle WT. Incidental intracranial hemorrhage after uncomplicated birth: MRI before and after neonatal heart surgery. *Neuroradiology*. 2003; 45:253–258. [PubMed: 12687311]
9. Ferencz C, Rubin J, McCarter R, Brenner JL, Neill CA, Perry LW, Hepner SI, Downing JW. Congenital heart disease: Prevalence at Live birth. The Baltimore-Washington Infant Study. *Am J Epidemiol*. 1985; 121:31–36. [PubMed: 3964990]
10. Lurie IW, Kappetein AP, Loffredo CA, Ferencz C. Non-cardiac malformations in individuals with outflow tract defects of the heart: the Baltimore-Washington Infant Study (1981-1989). *Am J Med Genet*. 1995; 59:76–84. [PubMed: 8849016]

Table 1

Demographic Information

	N = 141
Age, days	2 (1 - 31)
Gestational Age, weeks	38 (37 - 39)
Gestational Age $\leq$ 36 weeks, n (%)	28 (20)
Sex, M/F	74/67
Hospital Mortality, n (%)	15 (11)
Cardiac Diagnosis, n (%)	
CTD	53 (36)
SD	26 (18)
SV	25 (18)
LSO	20 (14)
RSO	4 (3)
Other	12 (8)

CTD: Conotruncal Defect; FISH: Fluorescence in situ hybridization; LSO: Left-sided Obstructive Lesions; RSO: Right-sided Obstructive Lesions; SD: Septal Defects; SV: Single-Ventricle

Table 2

Genetic, Renal and Head Ultrasound Results

	CTD (53)	SD (26)	SV (25)	LSO (20)	RSO (4)	Other (12)
Karyotype						
Performed, n (%)	45 (85)	22 (85)	24 (96)	16 (80)	4 (100)	8 (67)
Abnormal, n (%)	3 (7)	8 (36)	4 (17)	1 (6)	0	1 (12)
FISH for 22q11.2						
Performed, n (%)	44 (83)	12 (46)	21 (84)	14 (70)	4 (100)	8 (67)
Abnormal, n (%)	4 (9)	0	0	1 (7)	0	0
RUS						
Performed, n (%)	43 (81)	16 (61)	21 (84)	18 (90)	3 (75)	11 (92)
Abnormal, n (%)	8 (19)	6 (37)	4 (19)	6 (33)	2 (67)	3 (27)
HUS						
Performed, n (%)	48 (91)	16 (61)	24 (96)	19 (95)	4 (100)	11 (92)
Abnormal, n (%)	13 (27)	4 (25)	4 (17)	3 (16)	1 (25)	2 (18)
Patients with Abnormal Tests (%) *	23 (43)	15 (58)	11 (44)	11 (55)	2 (50)	5 (42)

* Nine patients had more than one abnormal test 5, see Table 6 for details CTD: Conotruncal Defect; FISH: Fluorescence in situ hybridization; HUS: Head Ultrasound; LSO: Left-sided Obstructive Lesions; RUS: Renal Ultrasound; RSO: Right-sided Obstructive Lesions; SD: Septal Defects; SV: Single-Ventricle

Table 3

Chromosomal Abnormalities among 119 Karyotype Results

	N (%)	Groups
47, XX, + 21	5 (4)	SD:4, CTD:1
47, XY, + 21	3 (2.5)	SD:2, SV:1
45,XO	1 (1)	LSO
46, XX, del (4) (p14)	1	SD
46, XX, der (21;21) (q10;q10)	1	CTD
46, XY, del (8) (p23.1p23.2)	1	SV
46, XY, der (18) t (10;18)	1	SV
46, XY, der (18) t (3;18) (q25.2;p11.2) mat	1	SD
47, XX, + idid (mar)	1	Other
47, XY, + mar mat	1	SV
46, XY, rea (11) (p15)	1	SD

CTD: Conotruncal Defect; LSO: Left-sided Obstructive Lesions; RSO: Right-sided Obstructive Lesions; SD: Septal Defects; SV: Single-Ventricle

Table 4

Baseline Renal Abnormalities among 112 Ultrasounds

	N (%)
Pelviectasis	12 (11)
Single Kidney	4 (3.5)
Nephrocalcinosis	4 (3.5)
Hypoplasia	3 (2.5)
Horseshoe Kidney *	3 (2.5)
Hydronephrosis	2 (2)
Loss of Cortical Differentiation	2 (2)
Pelvic Kidney	1 (1)
Renal Cyst	1 (1)

* One patient had both horseshoe kidney and pelviectasia

Table 5

Baseline Intracranial Abnormalities among 122 Ultrasounds

	N (%)
Grade I Intraventricular Hemorrhage	8 (6.5)
Increased Extra-axial Fluid	6 (5)
Absent Corpus Callosum	3 (2.5)
Hydrocephalus	2 (1.5)
Choroid Plexus Cyst	2 (1.5)
Cerebral Cyst	2 (1.5)
Periventricular Cyst	1 (1)
Cerebral Edema	1 (1)
Subdural Hemorrhage	1 (1)
Dandy Walker Malformation	1 (1)

Table 6**Patients with Multiple Extracardiac Abnormalities**

Lesion	Genetic Testing	RUS	HUS
CTD	46 XX (der 21;21) (q10;q10)	Pelviectasia	Normal
CTD	22q11 deletion	Nephrocalinosis	Increased extra-axial fluid
CTD	Normal	Loss of CMD	Hydrocephalus
CTD	Normal	Pelviectasia	Grade I IVH
SD	46 XX del (4)(p14)	Pelviectasia / VUR III	Cerebral Cyst
SD	Normal	Single Kidney	Increased extra-axial fluid
SV	Normal	Hydronephrosis	Increased extra-axial fluid
Other	47 XX idid (mar)	Pelviectasia	Normal
RSO	Normal	Pelviectasia	Dandy-Walker Malformation

CMD: Corticomedullary Differentiation; HUS: Head Ultrasound; IVH: Intraventricular Hemorrhage; RUS: Renal Ultrasound; VUR: Vesicoureteral Reflux