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Universal Screening for Extracardiac Abnormalities in Neonates with Congenital Heart Disease

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Abstract

Extracardiac or genetic abnormalities (EGA) represent a factor in the morbidity of patients with congenital heart disease. We evaluated the way neonates with CHD are screened at our institution and determined the yield for the screening tests. We reviewed the charts of 223 neonates with structural CHD. Subjects were categorized into 6 groups: univentricular, left-sided obstructive lesions, right-sided obstructive lesions, septal defects, conotruncal defects (CTD), and other. We reviewed which patients underwent cranial ultrasonogram (CUS), abdominal ultrasonogram (AUS), and/or genetic studies (GS) as well as their results. There was a high prevalence of EGA in each group by CUS (32% to 42%), AUS (32% to 69%), and GS (10% to 60%). There was

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considerable variability in the proportion within each group that underwent screening tests, and the consistency of screening often was not congruent with the likelihood of abnormal results. Approximately 50% of our patients had ≥1 EGA identified, resulting in a cost-yield ratio of $4,508/patient with EGA. Screening for EGA at our institution is not uniform and is often at odds with the prevalence of such patients. Given the high prevalence of EGA, we advocate for a universal screening program for neonates with CHD using cranial/abdominal ultrasonography and genetic testing.

Keywords

Congenital heart disease; Extracardiac; Screening

The presence of extracardiac or genetic abnormalities (EGA) constitutes an important determinant of morbidity and mortality of patients with congenital heart disease (CHD) [1, 2, 9, 16, 18]. Although it is known that there is a higher incidence of extracardiac [3–8, 11, 12, 14] and genetic [10, 13, 17] abnormalities among these patients compared with normal controls, the results of most studies that have examined this issue are outdated because they employed testing modalities that differed in sensitivity and specificity compared with current clinical studies today. Although the indications for performing screening tests for neontes with EGA have also evolved, they are not standardized and vary widely both within and among institutions. We recently showed that in prenatally diagnosed patients, the coexistence of cardiac and chromosomal abnormalities is a significant predictor of parental intention to treat [19].

In this observational study, we sought to examine our center's practice of screening for EGA in neonates who had been prenatally diagnosed with CHD (1) to determine the yield of our screening tests among specific cardiac diagnostic categories and (2) to perform a cost-yield analysis.

Patients and Methods

Study Population

The Medical University of South Carolina (MUSC) is the primary center for The Children's Heart Program of South Carolina, which serves the entire population of the state. Nearly all fetuses in South Carolina who are diagnosed with CHD are followed-up by their local pediatric cardiologists, and those who may require neonatal heart surgery are referred to MUSC for prenatal evaluation, delivery, and postnatal management. In addition to this referral population, we provide primary fetal cardiology services, and MUSC serves as the sole site for delivery in all such pregnancies where the mother lives in the vicinity of Charleston regardless of whether neonatal heart surgery is anticipated. The universal indication for performance of fetal echocardiograms in our echocardiography laboratory is a positive screen suggestive a cardiac abnormality, either by our colleagues in the Maternal Fetal Department at MUSC or by local cardiologists. This screening could include a routine obstetric ultrasound, amniocentesis, laboratory screening, or first-degree family history of critical CHD. Since July 1998, all prenatally diagnosed patients with heart defects have been

listed in an institutional database. All patients who were diagnosed with congenital heart defects based on fetal echocardiography between August 1998 and September 2007 and who were subsequently born at MUSC were identified using this database, and they form the study population. Patients who were prenatally diagnosed with cardiac tumors or arrhythmias in the setting of a structurally normal heart were excluded.

Study Design

This retrospective medical review received Institutional Review Board approval from MUSC. Patients were categorized by diagnosis (based on postnatal transthoracic echocardiography) into six groups: functionally univentricular (single-ventricle [SV]) heart, left-sided obstructive (LSO) lesions, right-sided obstructive (RSO) lesions, septal defects (SD), conotruncal defects (CTD), and other. Some of the diagnoses were categorized into more than one group, but efforts were made to avoid redundancy. For example, hypoplastic left heart syndrome was included in both: SV and LSO, while tetralogy of Fallot was included in the RSO and conotruncal groups, it was not included in the SD group.

We examined the medical records to determine which patients underwent cranial ultrasonogram (CUS), abdominal ultrasonogram (AUS), and prenatal and/or postnatal genetic studies (GS); the latter included karyotype and fluorescent in situ hybridization for 22q11 deletion. If these tests were performed, the results were noted. Each neonate's birth weight and gestational age at birth were recorded as well.

For patients in whom an abnormality was identified by either CUS or AUS, a neonatologist (S. A. T.) who was blinded to the cardiac diagnoses classified the abnormality into one of three groups: significant, marginally significant, or insignificant. An abnormality was classified as significant if it would generally result in a change in management or follow-up. It was classified as marginally significant if it was considered clinically relevant, but would not result in a change in management or follow-up, and it was classified as insignificant if it was considered a normal variant, not clinically relevant, or secondary to medical management.

Findings on CUS that were classified as significant included hydrocephalus, agenesis of the corpus callosum, Dandy Walker malformation, intraparenchymal hemorrhage, intraventricular hemorrhages greater than or equal to grade 2, and agenesis of the vermis. Marginally significant CUS findings included vascular calcifications (found in both the thalamus and lenticulostriate regions), thalamostriate vasculopathy, and multiple cysts. CUS findings classified as insignificant included accessory intraventricular membrane, grade 1 hemorrhages, solitary cysts, choroid plexus cysts, linear septations, and mild brachycephaly.

Findings on AUS that were classified as significant included heterotaxy (comprising malrotation, asplenia, polysplenia, and midline liver), single kidney, multicystic kidney, renal dysplasia, bilateral hydronephrosis, horseshoe kidney, liver hemangiomas, and hepatic venous fistula. Marginally significant AUS findings included hypoplastic kidneys, renal cysts, extrarenal pelvis, ureterectasis or pelvocaliectasis, unilateral hydronephrosis, atypical hepatic venous drainage, and undescended testicle. Insignificant AUS findings included mild ascites, nephrocalcinosis, stasis nephropathy, adrenal hemorrhage (asymptomatic

patient), enlarged adrenal glands, dilated hepatic veins, intrahepatic gas, intrahepatic fluid collection, and pericholecystic fluid. Abnormalities identified on GS included trisomy 21, trisomy 18, trisomy 13, microdeletion 22q11, 45 XO, and a variety of less common deletions or translocations.

Statistical Analysis

Chi-square analyses were used to compare the performance and results of each screening test between groups. Each of the six diagnostic categories was analyzed individually and compared with the remainder of the groups. For example, patients with lesions categorized as LSO lesions were compared with patients without LSO lesions, and so on. Student *t* test was used to evaluate the association between continuous variables (weight and gestational age) and the performance and results of each screening test. All statistical tests were two-sided, and type I error was controlled for each test at a level of $P = 0.05$. Analyses were performed with SAS (version 9.1; Cary, NC).

Results

During the time period studied, 230 newborns with a presumed cardiac diagnosis (by fetal echocardiography) were born. Six of these newborns were found to have normal cardiac anatomy by transthoracic echocardiography, and one infant with trisomy 18 died soon after delivery. The remaining 223 subjects were studied (Table 1). They underwent 423 diagnostic studies (134 CUS, 131 AUS, and 158 GS). Of these 423 tests, 146 (33%) were abnormal. Of all patients studied, 52% had at least 1 abnormal test result. After excluding results classified as insignificant, 46% had at least 1 abnormal test result. Of the study population of 223 subjects, 193 patients (87%) underwent at least 1 study.

The frequency with which tests were obtained varied widely. Of the 223 neonates, 134 (60.1%) underwent CUS. Among those, 36.6% were abnormal, with 20.9% having abnormalities classified as significant or marginally significant. Among the total of newborns screened who underwent CUS, 36 (26.8%) had a gestational age <37 -weeks at delivery. Among those, 44% had abnormalities, with 27% having abnormalities classified as significant or marginally significant. The difference in the incidence of significant or marginally significant abnormalities between newborns with gestational age <37 weeks was not significantly different from those with gestational age >37 weeks ($P = 0.24$). One hundred thirty-one neonates (58.7%) underwent AUS. Among those, 41.2% had abnormalities, with 36.6% having abnormalities classified as significant or marginally significant. One hundred fiftyeight neonates (70.9%) underwent GS. Among those, 27.2% had abnormalities.

Individual results from each diagnostic group are listed in Table 1. Further analysis showed that compared with those with a functionally biventricular heart, those with functionally SV hearts were three times more likely to undergo CUS ($P < 0.001$) and 3.5 times more likely to undergo AUS ($P < 0.001$). However, among those tested, there was no difference in the percentage of abnormal results ($P = 0.61$ and $P = 0.57$, respectively). Those with functionally SV hearts were 48% less likely to undergo GS ($P = 0.02$), 18% less likely to

undergo amniocentesis ($P < 0.001$), and 87% less likely to have genetic abnormalities than those with biventricular physiology ($P < 0.001$).

Compared with those without LSO lesions, patients with LSO lesions were 3.4 times more likely to undergo CUS ($P < 0.001$) and 2.2 times more likely to undergo AUS ($P < 0.001$). However, among those tested, there was no difference in the percentage of abnormal results ($P = 0.78$ and $P = 93$, respectively). Those with LSO lesions were 50% less likely to undergo GS ($P = 0.02$) and 64% less likely to undergo amniocentesis ($P = 0.002$). However, there was no difference in the incidence of genetic abnormalities among those that were tested compared with patients without LSO lesions ($P = 0.11$).

Compared with other groups, neonates with conotruncal defects were no more likely to undergo CUS and AUS ($P = 0.95$ and $P = 0.43$, respectively). Although they were 3.3 times more likely to undergo GS ($P = 0.01$), there was no difference in the percentage who underwent amniocentesis ($P = 0.17$). Among those tested, there was no difference in the percentage of abnormal CUS or AUS results or genetic abnormalities identified compared with those without conotruncal defects ($P = 0.84$, $P = 0.57$, and $P = 0.31$, respectively).

Compared with other groups, neonates with RSO lesions were not more likely to undergo CUS or AUS ($P = 0.42$ and $P = 0.15$, respectively), but they were 2.1 times more likely to undergo GS ($P = 0.05$). Among those who underwent ultrasonogram or GS, there was no difference in the percentage with abnormal results compared with patients without RSO lesions ($P = 0.54$, $P = 0.32$, and $P = 0.11$, respectively). There was no difference in the percentage who underwent amniocentesis ($P = 0.47$).

Neonates with septal defects were 70% less likely to undergo CUS ($P = 0.001$) and 62% less likely to undergo AUS ($P = 0.01$). There was no difference in the percentage who had abnormal CUS ($P = 0.70$), but patients with septal defects were 3.7 times more likely to have abnormal AUS than those without septal defect ($P = 0.03$). Those with septal defects were 3.8 times more likely to undergo GS ($P = 0.01$) and 5.9 times more likely to undergo amniocentesis ($P < 0.001$). Among those tested, patients with septal defects were 6.7 times more likely to have a genetic abnormality ($P < 0.001$).

Cost-Yield Analysis

At our institution, the cost of performing these three screening tests is $2,254/patient (cranial ultrasonogram $548, abdominal ultrasonogram $866, and karyotype $840, including both technical and professional fees). Because approximately 50% of our tested patients had at least one significant abnormality identified by these tests, the cost of identifying each significant abnormality was $4,508/patient.

Discussion

The current study sheds some light on the occurrence of abdominal, intracranial, and genetic abnormalities in a series of contemporary live-born neonates with prenatally diagnosed congenital heart defects during a 9-year period. Because the performance of tests was variable, it is not possible to derive true incidence numbers from our data. It is likely that in

some cardiac diagnostic subgroups, more than in others, tests were ordered only when an abnormality was suspected clinically. For example, patients with septal defects were significantly less likely to undergo AUS than all other patients, but they were significantly more likely to have abnormal results from this test. Tests may also have been obtained based on known associations or in scenarios perceived to be high risk. For example, >87% of patients with septal defects or conotruncal abnormalities underwent GS, which is unsurprising given the known associations with trisomies 13, 18, and 21 as well as 22q11 deletions. More than 70% of patients with functionally SV hearts or with LSO lesions underwent CUS and AUS, probably reflecting heightened concerns in caring for this group of patients who almost always require neonatal cardiac surgery. Although frequency of the performance of tests was widely variable, frequency of the detection of abnormalities was remarkably consistent across groups, except for patients with functionally SV hearts, among whom the incidence of genetic abnormalities (9.5%) was lower than in all other patients.

The findings of this study have stimulated our program to develop a practice guideline that calls for uniform performance of these tests in all neonates with significant heart defects. This should allow us to provide robust estimates of incidence in the future. Notwithstanding the impressive intracenter variability of the performance of these tests, the incidence of abnormalities is quite high. This has many farreaching implications and raises important questions.

Given the series of systemic perturbations that are implicit in neonatal cardiac surgery, it is reasonable to assume that the presence of extracardiac abnormalities may have an important impact on surgical morbidity and mortality. In the immediate term, the results of these tests have important implications for counseling families as well as for risk stratification and perioperative management. To systematically analyze the impact of extracardiac abnormalities, we plan to study risk-adjusted surgical outcomes among the cohort of patients from the current study who underwent surgery before discharge.

The findings of the cost-yield analysis are provocative. Although the $4,508 cost of detection of each abnormality is significant, it should be evaluated in light of the financial, emotional, and medical costs of potentially not detecting important abnormalities among neonates who are already known to have a major defect in one organ system. The majority of abnormalities on AUS were either renal or consisted of findings associated with heterotaxy. The cost of a renal ultrasonogram in our institution is $606, which is $260 lower than the cost of AUS. Because echocardiography is quite reliable at identifying markers of heterotaxy, a potential savings of $520/detected abnormality could be realized by obtaining renal ultrasonogram instead of AUS, other than in cases of visceroatrial heterotaxy. This could potentially decrease the cost of detection of each abnormality to $3,988. For comparison, a recent analysis was performed by Schoen et al. [15] to evaluate the cost-benefit ratio for universal newborn screening for inborn errors of metabolism. The stated incidence of having one of the six disorders screened for in their program was 24.5/100,000. The cost for each newborn screen was $15, resulting in a cost-to-detection ratio of $61,224 for each true positive, not including the costs of false-positive results. Given that newborn screening for inborn errors of metabolism is a well-accepted practice, the screening program proposed by this study is fairly reasonable from a cost-yield perspective. A more detailed

cost-benefit analysis of this screening program, taking into account possible outcomes resulting from delayed diagnosis, is planned at our institution.

Conclusion

Our data suggests that a universal screening program, using CUS and AUS combined with a prenatal or postnatal karyotype (plus or minus florescence in-situ hybridization for microdeletion 22q11 in patients with lesions known to be associated with DiGeorge syndrome) is a reasonable strategy in neonates who require congenital heart surgery. Further analysis of the surgical outcomes of patients with certain extracardiac abnormalities, along with a detailed cost-benefit analysis of this universal screening program, is indicated.

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Table 1

Summary of findings by diagnostic group

Lesion type	No.	CUS performed[a]	Abnormal CUS[b]	Significant CUS findings[c]	AUS performed[a]	Abnormal AUS[b]	Significant AUS findings[c]	Genetic study performed[a,d]	Amniocentesis performed[a]	Abnormal GS[b]
All	223	134 (60.1)	49 (36.6)	28 (20.9)	131 (58.7)	54 (41.2)	48 (36.6)	158 (70.9)	80 (35.9)	43 (27.2)
SV	101	75 (74.3)	26 (34.7)	17 (22.7)	75 (74.3)	29 (38.7)	26 (34.7)	63 (62.4)	20 (20.2)	6 (9.5)
LSO	69	54 (78.3)	18 (33.3)	12 (22.2)	49 (71.0)	20 (40.8)	17 (34.7)	41 (59.4)	14 (20.6)	7 (17.1)
CTD	38	23 (60.5)	8 (34.8)	4 (17.4)	20 (52.6)	7 (35.0)	6 (30.0)	33 (86.8)	17 (44.7)	11 (33.3)
RSO	56	31 (55.4)	10 (32.3)	6 (19.4)	28 (50.0)	9 (32.1)	8 (28.6)	45 (80.4)	22 (39.3)	8 (17.8)
SD	34	12 (35.3)	5 (41.7)	3 (25.0)	13 (38.2)	9 (69.2)	8 (61.5)	30 (88.2)	24 (70.6)	18 (60.0)

CTD conotruncal defects, *CUS* cranial ultrasonogram, *SD* septal defects

[a] N (% of patients in the group)

[b] N (% of patients in whom the study was performed)

[c] N (% of patients in whom the study was performed, including those categorized as significant or marginally significant)

[d] Includes both amniocentesis and postnatal GS