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Abnormal Microarray, Clinical Outcomes and Surgical Risk Scores in Young Children with Cardiac Disease

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Abstract

Introduction.—The clinical implications of abnormal chromosomal microarray (CMA) remain unclear for children less than 1 year of age with critical heart disease. Our objective was to determine whether abnormal CMA was related to surgical severity scores or to pre-determined clinical outcomes, including cardiac arrest.

Methods.—Retrospective review of children under 1 year of age admitted to a pediatric cardiac intensive care unit from December, 2014 to September, 2017. Associations between CMA result and cardiac arrest, syndromic abnormalities, and extracardiac anomalies were evaluated. A simple and multivariable logistic regression model was used to analyze associations between STAT mortality category and CMA result.

Results.—The overall prevalence of abnormal microarray was 48/168 (29%), with peak prevalence in AV septal defects and left-sided obstructive lesions. There was no statistical association between surgical severity scores and abnormal CMA (STAT 1/2 vs. 3+, odds ratio 0.56, p=0.196). Abnormal CMA was associated with a higher prevalence of cardiac arrest (5/48

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Conflicts of Interest

The authors have no conflicts of interest to report.

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Not applicable

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Not applicable

abnormal CMA vs. 2/120 normal CMA, p=0.02). Abnormal CMA was associated with a higher frequency of syndromic abnormalities (18/48 abnormal CMA vs. 13/120 normal CMA, p<0.001).

Conclusions.—There was a high prevalence of abnormal CMA findings in the pediatric cardiac population less than 1 year of age (29%), associated with cardiac arrest, but not associated with surgical risk score. The absence of a standardized protocol for ordering a CMA in the setting of congenital heart disease results in a highly variable prevalence data.

Keywords

pediatric; congenital heart disease; chromosomal microarray; cardiac arrest; surgical risk score

INTRODUCTION

Congenital heart disease is the leading cause of death related to birth defects and has been associated with a chromosomal abnormality in 12-30% of cases.[1-4] There is no consensus on which clinical presentations are associated with the highest prevalence of abnormal chromosomal microarray (CMA). For example, some studies show that septal defects have the highest diagnostic yields.[5-7] Others have found that right ventricular outflow tract obstructions (RVOTO) have the highest diagnostic yield.[8] Few studies have linked CMA abnormalities to cardiac clinical outcomes in the first year of life. Most existing research on the prevalence of abnormal microarray genetic testing in congenital heart disease is based on the developmental biology of cardiac malformations. However, the clinical severity of a disease is not easily determined by the developmental biology categorization, so correlating CMA with clinical outcomes research has been challenging. For example, the clinical severity of a small primum atrial septal defect is usually mild compared to an unbalanced atrioventricular canal, even though both arise from endocardial cushion defects.

The goal of this retrospective study was to link abnormal CMA and clinical cardiac outcomes. We used cardiac surgical severity scores as a classification system to test this hypothesis as well as clearly defined cardiac outcomes, such as a cardiac arrest during admission. We included only children admitted at less than 1 year of life because the surgical options are most predictable in the first year of life.

METHODS

All patients less than 1 year of age admitted to our tertiary, pediatric cardiac intensive care unit (CICU) from 12/1/14 to 9/1/17 were identified from the Pediatric Cardiac Critical Care Consortium (PC4) database for this retrospective review study. Only the first admission was counted for each patient so that each patient was only included once. The presence of syndromic abnormalities (a characteristic group of signs and symptoms) was determined by the attending physician or subspecialist on service, as recorded in the PC4 database. Information on clinical outcomes was obtained from the PC4 database and by direct review of electronic medical records (EPIC, Verona, WI). The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery (STAT) mortality category, the Risk Adjustment for Congenital Heart Surgery (RACHS) risk category, and data on surgical complications were obtained from the Society of Thoracic Surgeons (STS) database. In

patients with multiple scores from different surgeries during the same admission, the surgery with the highest score was recorded. Results from chromosomal microarray (CMA) tests were obtained from medical records. Microarray results are stable genetic results (not age-dependent). Therefore, all CMA results were included in the analysis, independent of the date of CMA collection. All data were centralized in the REDCap (Research Electronic Data Capture) system hosted at Northwestern University Clinical and Translational Sciences Institute. Appropriate human subjects approval was obtained from our Institutional Review Board.

Race was self-reported by the parent or guardian at the time of registration. Congenital heart disease diagnoses were grouped based on the National Birth Defect Prevention Study classification system with additional categories for arrhythmia and cardiomyopathy.[9] Hypoplastic left heart syndrome (HLHS) with single ventricle physiology was classified separately from left ventricular disease with biventricular physiology.

Whole genome CMAs were used to detect copy number variants. The CMA result was a dichotomous variable classified as either abnormal or normal. Abnormal CMA results occurred when one or more missing or extra chromosomal segments were present.[10] The Genetic Testing Registry (GTR) was used to identify genes that occurred in abnormal CMA regions.[11] Copy number imbalances deemed to be benign or likely benign by current guidelines were excluded from analysis.[12]

CMAs were obtained during clinical care and were performed in a CLIA-certified lab. The lab performed array comparative genomic hybridization analysis with an oligonucleotide array designed to detect copy number imbalances (losses or gains) of specific chromosomal regions and across the genome. Quality indicators and sex chromosome internal controls were reviewed in each case to ensure successful hybridization. Only 5/48 abnormal CMA results were classified as variants of uncertain significance (VUS). These were classified as abnormal for the main analysis. As a sensitivity analysis, VUS were also dichotomized as “normal”. Statistical conclusions were unchanged with the alternative classification, including no effect on the cardiac arrest analysis. All statistical analysis was performed in the statistical software R version 3.5.1 (R Core Team, 2018), and an alpha level of 0.05 was considered for all hypothesis testing.

Primary analysis considered an association between STAT score and CMA result. The analytic cohort for the primary analysis included all patients in the PC4 database with CMA results and a STAT mortality category. The cohort for the secondary analyses included all patients in the PC4 database with CMA results (STAT score was not required for secondary analyses). Descriptive statistics summarized demographic and clinical variables overall and by CMA result. Associations between demographics and clinical outcomes with CMA results as well as associations of cardiac arrest with CMA results and history of cardiac surgery were tested using chi-squared tests or a Fisher’s exact test, in the case of low cell counts. For the primary analysis, a logistic regression model was used to assess the association between STAT mortality category and CMA result. Specifically, we considered a dichotomized version of the STAT mortality category due to low cell counts at individual score levels. Sensitivity and specificity were estimated at each possible cut-point for STAT

mortality category, and the optimal threshold for dichotomization was determined to be less than or equal to 2 via Youden's index. A multivariable logistic regression model was constructed to control for sex and race as biologically plausible confounders in the multivariable model. A Hosmer-Lemeshow test was used to assess the goodness of fit. Similar methods were employed for the second independent variable of interest, RACHS risk category, where the cutpoint was also found to be less than or equal to 2.

RESULTS

Between December 2014 and September 2017, 540 patients less than 1 year of age were admitted to the CICU. Of those, chromosomal microarray (CMA) was performed in 168 (Figure 1). An abnormal CMA was present in 48/168 patients (28.6%). The median age at admission was 1 day of life (interquartile range 0–18 days) for those who had a CMA. There was no difference in the prevalence of abnormal CMA results by gender (24/95 male vs. 24/73 female, p=0.28) or by dichotomized self-report of race (26/87 white vs. 22/80 non-white, p=0.73, Table 1). All abnormal microarray results from this study are reported in Online Resource 1.

The presence of syndromic abnormalities was defined on clinical grounds by the treating clinician. An abnormal CMA was associated with a higher frequency of syndromic abnormalities. Of those with an abnormal CMA, 18/48 (37.5%) had a syndromic abnormality while 13/120 (10.8%) patients with a normal CMA had a syndromic abnormality ($p<0.001$).

We examined associations between microarray result and clinical outcomes (Table 2). Cardiac arrest occurred in 5/48 patients with an abnormal CMA (10.4%); whereas cardiac arrest occurred in only 2/120 patients with normal microarray (1.7%, p=0.02). Cardiac arrest was not associated with history of cardiac surgery before or during the first hospital admission at our institution (p=0.97) or availability of CMA results (p=0.39). Table 3 lists the abnormal CMA results in patients with cardiac arrest. We analyzed each CMA abnormality to determine if the abnormality encompassed genes associated with structural cardiac abnormalities, cardiomyopathy or rhythm disorders. None of the genes in regions of CMA abnormalities were associated with known genotype-phenotype correlations for cardiac disease or arrhythmia.

STAT mortality category was available in 111/168 patients with CMA results. There was no trend in the prevalence of abnormal CMA across STAT classifications (Figure 2). An unadjusted model found no statistical association between STAT mortality category (dichotomized as 1, 2 vs. 3, 4, 5) and abnormal CMA (odds ratio 0.57, CI_{95} 0.23-1.36, p=0.2). A multivariable model including race and sex as possible confounders confirmed this finding (odds ratio 0.56, CI_{95} 0.23-1.35, p=0.2). As a sensitivity analysis, the same tests were performed using RACHS risk category (dichotomized as 1,2 vs. 3, 4, 5) as the independent variable of interest. Similar results were found in the 107/168 patients who had both a RACHS risk category and a CMA (odds ratio 0.65, CI_{95} 0.26-1.69 p=0.37, Online Resource 2).

The frequency of abnormal CMA results varied by diagnosis (Table 4). The prevalence of abnormal CMA was over 25% in only 5 classes of congenital heart disease: right and left outflow tract obstruction, pulmonary venous anomalies, conotruncal defects, and atrioventricular septal defects (AVSD), although analysis was limited by small cell counts in AVSD.

DISCUSSION

In our primary analysis, increased clinical severity of surgical disease was not associated with an increased prevalence of CMA abnormalities. The lack of an association between STAT mortality category and abnormal CMA among children less than 1 year of age who require surgery continues to reinforce the hypothesis that in the circulatory system, developmental biology provides a stronger framework for understanding chromosomal abnormalities than the surgical severity of the lesion.

In our retrospective analysis of patients in whom a CMA was obtained, abnormal CMA was associated with a higher risk of cardiac arrest during hospitalization. This supports existing data by Alten and colleagues, who found an odds ratio of 1.36 in favor of cardiac arrest in children with “any chromosomal abnormality” using registry methods.[13] The current study provides new data by analyzing the specific genes associated with each CMA finding. In this cohort, cardiac arrest was not associated with disruptions in known genes contributing to structural heart disease, cardiomyopathy or channelopathy. The absolute numbers of cardiac arrests in our study are low; however, our data support the important hypothesis that genetic abnormalities with low individual effect sizes contribute an incremental risk for cardiac arrest.

Our data also support a large genotype-based study in children with congenital heart disease. A recent study of 2,517 patients with congenital heart disease and whole exome sequencing identified copy number variants at 15q11.2 as a potential association with reduced transplant-free survival.[14] While limited to a single observation, CMA in our study revealed a 15q11.2 deletion in one patient with cardiac arrest.

In summary, the association between abnormal CMA and risk for cardiac arrest is important because a rapid and cost-effective test such as CMA may improve clinical outcomes during inpatient care if patients at increased risk of cardiac arrest can be identified early in the patient’s CICU care.

Finally, we tabulated the distribution of abnormal CMA results among structural congenital heart diagnoses. We provide detailed relationships between diagnoses and abnormal CMA in this cohort. For example, the prevalence of abnormal CMA in the setting of pulmonary venous anomalies was 40% in our cohort, matching the data in Ahrens *et al*, who also found a prevalence of 40% in a cohort of 347 cardiac patients. However, the prevalence in other studies has been lower.[6,7] The wide variation in reported results has inhibited the development of a single CMA protocol in cardiac intensive care units. The next step should be a coordinated, prospective effort to evaluate CMA in the setting of children less

than 1 who present to cardiac intensive care units with close evaluation of clinically-relevant outcome measurements.

The growing number of small, single-center studies evaluating CMA in the CICU suggests that the time is ripe to interrogate a larger network to make a definitive, prospective conclusion about the value of CMA in the CICU. This is especially important because some centers have begun to order CMA routinely. While it is not yet standard of care in every CICU, CMA has begun to be labelled as standard of care and can replace karyotype in many settings.[2,15,16] The data in the current study are a step toward establishing the clinical utility for CMA in neonatal congenital heart disease. We reinforce a preliminary association between abnormal CMA and cardiac arrest during hospitalization. We demonstrate that surgical risk scores were not statistically linked with abnormal CMA and provide additional preliminary data about lesion-specific prevalence.

The generalizability of these data are limited by the methods of a single-center retrospective study. While this study adds new genotype analysis in cardiac arrest, our data are potentially influenced by the lack of a single ordering protocol for CMA in our cardiac intensive care unit during this period. Thus, differences in practice patterns among individual providers may have influenced our retrospective analysis.

CONCLUSIONS

There was a high prevalence of abnormal CMA findings in the pediatric cardiac population less than 1 year of age (29%), linked to cardiac arrest outcomes but not associated with surgical risk score. The absence of a standardized protocol for ordering a CMA in the setting of congenital heart disease results in highly variable prevalence data.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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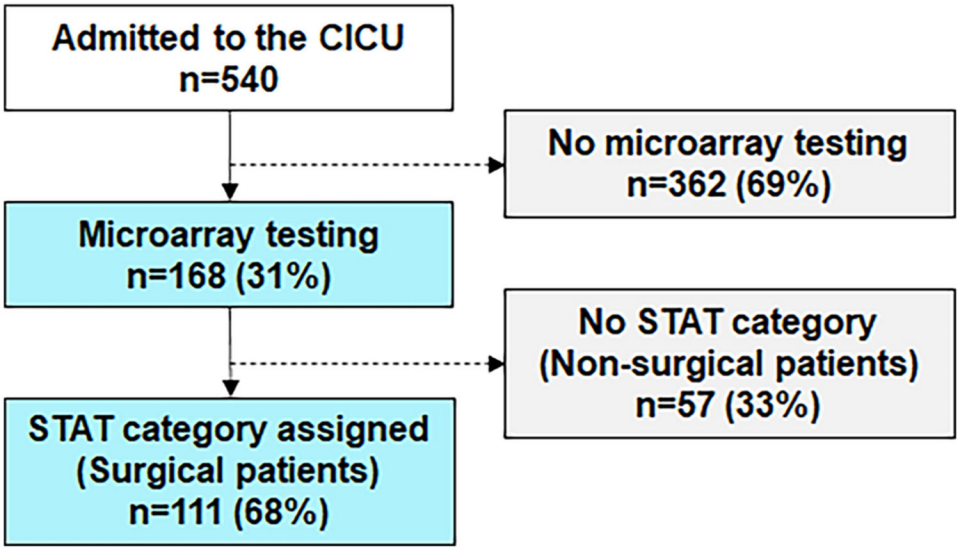

Fig 1.

Frequency of microarray testing in the cardiac intensive care unit. All patients admitted to the CICU under 1 year of age were evaluated. Microarray testing was at the discretion of the attending intensivist. STAT mortality category is a risk score developed for congenital heart surgery and was assigned based on the highest STAT mortality category assigned during the hospitalization. CICU = cardiac intensive care unit; STAT = The Society of Thoracic Surgeons-European Association for Cardio-Thoracic Surgery

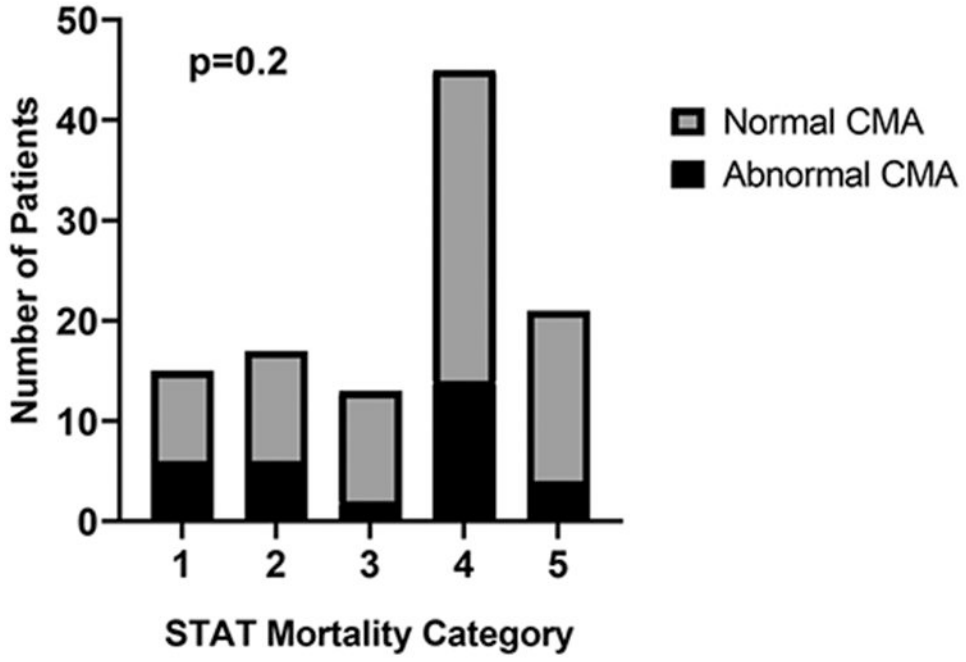

Fig 2.

Distribution of chromosomal microarray by STAT mortality category. Results of microarray analysis are presented across STAT mortality category (1 = lowest severity; 5 = maximum severity). The dark shading represents the frequency of abnormal CMA results (range 15-40% of cases within mortality category). The distribution of abnormal CMA tests did not significantly change across STAT mortality category (p=0.2).

Table 1:

Demographics and primary outcome comparison

Variable	Total=168	Abnormal CMA (48)	Normal CMA (120)	P-Value
Admission Age in Days, median (IQR)	1.0 (0.0-17.5)	2.0 (0.0-97.5)	1.0 (0.0-10.5)	0.14
Sex				
Male	95	24	71	0.28
Female	73	24	49	
Race (%)				
Caucasian	90 (53.6)	27 (56.3)	63 (52.5)	
Hispanic/Latino	46 (27.4)	9 (18.8)	37 (30.8)	0.34
African American	19 (11.3)	7 (14.6)	12 (10.0)	
Asian	9 (5.4)	4 (8.3)	5 (4.2)	
Other	53 (31.5)	12 (25.0)	41 (34.2)	
CICU Length of Stay in Days, median (IQR)	8 (3-17)	7 (2-16)	9 (3-17)	

Table 2:

Associations Between Clinical Outcomes and Microarray Result

	level	Abnormal Microarray	Normal Microarray	p-value [a]
n		48	120	
Mortality (%)	No	43 (89.6)	108 (90.0)	0.999
	Yes	5 (10.4)	12 (10.0)	
Cardiac Cath (%)	No	36 (75.0)	82 (68.3)	0.601
	Yes	12 (25.0)	37 (30.8)	
	Missing	0 (0.0)	1 (0.8)	
Readmission within 30 days of discharge (%)	No	34 (70.8)	90 (75.0)	0.464
	Yes	8 (16.7)	22 (18.3)	
	Missing	6 (12.5)	8 (6.7)	
Cardiac Arrest (%)	No	43 (89.6)	117 (97.5)	0.021
	Yes	5 (10.4)	2 (1.7)	
	Missing	0 (0.0)	1 (0.8)	
Extracardiac Anomaly (%)	No	33 (68.8)	87 (72.5)	0.766
	Yes	15 (31.2)	33 (27.5)	
Syndromic Abnormality (%)	No	30 (62.5)	107 (89.2)	<0.001
	Yes	18 (37.5)	13 (10.8)	

[a] P-value from Chi-square or Fisher's exact test, as appropriate

Table 3.

Abnormal microarray results in children less than 1 with cardiac arrest

Diagnosis	Microarray Result
Hypoplastic Left Heart Syndrome	arr[hg19] 7q11.23(72,688,285-74,161,142)x3
Pulmonary Atresia	arr[hg19] Xq26.2(131,942,553-132,603,622)x3
Hypoplastic Left Heart Syndrome	arr[hg19] 15q11.2(22,628,639-23,178,762)x1
Conotruncal Defect	arr[hg19] 16p11.2(28,497,756-28,498,146)x1
Pulmonary Atresia	arr[GRCh37] 11q24.2q25(124,723,867-135,006,516)x3,14q32.33(104,133,013-107,349,540)x1

arr = microarray

hg19/GRCh37 = type of microarray test performed

Table 4:

Distribution of abnormal microarray among diagnoses

Diagnosis	Number of Cases	Abnormal CMA (% of cases)	Prior Reports of Abnormal CMA frequency [a]
Atrioventricular septal defect	2	1 (50)	0%[8], 25%[6], 33%[7], 53%[5]
Left ventricular outflow tract obstruction [b]	25	12 (48)	17%[7], 23%[6], 24%[5], 36%[8]
Anomalous pulmonary vein origin, connection, or other venous anomaly	5	2 (40)	0%[7], 0%[6], 40%[5]
Right ventricular outflow tract obstruction [c]	24	9 (38)	6%[7], 8%[5], 25%[6], 46%[8]
Conotruncal defect [d]	48	14 (29)	11%[7], 13%[8], 19%[5], 23%[6]
Hypoplastic left heart syndrome	26	6 (23)	
Septal defect [e]	10	2 (20)	23%[8], 33%[7], 48%[6], 56%[5]
Cardiomyopathy	5	1 (20)	
Other [f]	6	1 (17)	21%[6], 25%[7], 31%[5]
Single ventricle, other than HLHS	8	0 (0)	0%[8]
Patent ductus arteriosus	3	0 (0)	33%[8]
Arrhythmia	5	0 (0)	
Normal heart	1	0 (0)	
Total	**168**	**48/168 (29%)**	**14%** [7], **24%** [6], **28%** [8]

CMA, Chromosomal microarray; HLHS, hypoplastic left heart syndrome

[a] Citations numbers from References section

[b] Coarctation of the aorta, aortic stenosis, bicuspid aortic valve, interrupted aortic arch, aortic arch hypoplasia, Shone complex.

[c] Pulmonary stenosis or atresia, discontinuous pulmonary arteries, Ebstein anomaly of the tricuspid valve.

[d] Tetralogy of Fallot, transposition of the great arteries, double-outlet right ventricle, truncus arteriosus.

[e] Ventricular septal defect, atrial septal defect.

[f] Aortic aneurysm, high output cardiac failure due to vascular shunt, myocarditis, coronary anomalies, primary valve disease, pulmonary hypertension, vascular ring.