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Genetic Testing and Neurodevelopmental Follow Up in Patients with Conotruncal Abnormalities

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Abstract

Background: Genetic testing and post-operative neurodevelopmental evaluations are recommended for patients with conotruncal abnormalities. Early identification of genetic abnormalities and comorbidities can lead to early interventions.

Methods: This was a retrospective study of all patients, followed at our center, with isolated tetralogy of Fallot (TOF), interrupted aortic arch (IAA), and truncus arteriosus (TA) who underwent an index surgery between 2010 and 2016. Diagnosis, genetic testing occurrence and results, inpatient treatment, and follow up were analyzed.

Results: 170 patients were included. Only 104 (61%) patients had genetic testing; TOF patients had the lowest testing rates. Patients undergoing formal genetics consultation or admitted preoperatively had higher rates of genetic testing (90% and 78%, respectively). A total of 24 patients were identified as having 22q11 deletion. Only 30% of all patients regardless of genetic status received neurodevelopmental follow up.

Conclusion: Rates of genetic testing and neurodevelopmental follow up in patients with conotruncal abnormalities demonstrate a need for improvement. We have an opportunity to develop quality initiatives to improve testing rates, counseling, and ensuring appropriate neurodevelopmental follow up.

Keywords: 22q11, conotruncal abnormalities, neurodevelopment, DiGeorge syndrome, tetralogy of Fallot

Introduction

Congenital heart disease (CHD) is the most common birth defect and in most cases idiopathic. Genetic causes account for up to 35% of patients with CHD [1] are linked to increased operative risk and mortality [2]. One of the most common genetic abnormalities is a deletion in 22q11 [3], which affect 1 in 2,000-4,000 live births. This results in a wide spectrum of phenotypes including CHD, palatal abnormalities, immunodeficiency, hypoparathyroidism, dysmorphic facies, and developmental delay [4]. Conotruncal abnormalities are the most common cardiac defects and are found in 75% of patients with 22q11 deletions [3]. Deletions in 22q11 are found in 15% of patients with tetralogy of Fallot (TOF) [5], 50% with interrupted aortic arch (IAA), and 35% with truncus arteriosus (TA) [5]. Conoventricular ventricular septal defects (VSD) are associated with 22q11 deletion in roughly 5% of patients [5].

Genetic testing for 22q11 deletion is recommended for conotruncal defects, specifically TOF, IAA, and TA. Testing in patients with isolated VSD is not currently recommended [5]. The associated comorbidities should be evaluated particularly as they relate to growth and development. An understanding of a patient's genetic make-up is essential to providing anticipatory guidance for families and a key component in the preoperative surgical risk assessment [6]. Our primary aim is to describe our rate of testing in infants with conotruncal abnormalities. Our secondary aims were (1) to categorize which eligible patients received genetic testing and (2) to describe how these findings may lead to process improvements for genetic testing and follow up.

Materials and Methods

This was a retrospective study of all patients who underwent the following index case operations: tetralogy of Fallot with pulmonary stenosis (TOF/PS), TOF with absent valve, interrupted aortic arch (IAA), truncus arteriosus (TA), and TOF with pulmonary atresia (TOF/PA) at Children's National Health System between 2010 and 2016. Our institution went live with electronic medical records (EMR) in 2010, therefore, to have confidence regarding the presence of testing, we limited the date range and referred to the documentation in the EMR.

Chart reviews provided data on pre-operative admissions, genetic testing, subspecialty consults, and outpatient appointments while operative reports served as a secondary confirmation of diagnosis.

We excluded patients with additional cardiac diagnoses such as atrioventricular canal defects (AVC), pulmonary vein anomalies, and single ventricle variants. Also excluded were patients who had mortality during their inpatient course since our ability to assess for follow up or testing would not be complete. We excluded any patient who did not follow up with our institution. The lost to follow up group included any patient without a cardiology follow up appointment after their initial outpatient post-operative appointment.

Data analysis was performed using Microsoft Excel 2013 data package.

This was a project undertaken as a Quality Improvement Initiative at Children's National Health System and it did not constitute human subjects research. As such it was not under the oversight of the Institutional Review Board.

Results

There were 214 patients who met criteria. A total of 44 patients were excluded for further analysis based on mortality, loss to follow up, or additional complex cardiac anatomy. Therefore, our analysis included 170 patients for which we were able to collect inpatient and follow up data (Figure 1). For data analysis we separated the types of IAA. There were no IAA Type C in this cohort.

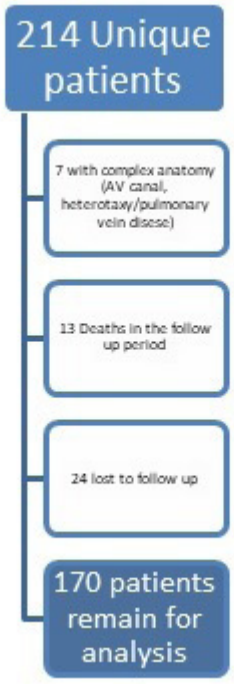

Figure 1. Eligible Participants

Most of the patients had a diagnosis of TOF/PS (Table 1). A total of 104 (61%) patients underwent genetic testing for 22q11 deletion. TOF/PS had the least number of patients receiving genetic testing despite being the most common diagnosis, only 55%. Fluorescence in situ Hybridization (FISH) was performed as primary testing until 2013. After that, microarrays were the dominant testing method. A deletion in 22q11 was found most commonly in our patients with IAA Type B. A total of 24 patients were identified with 22q11 deletions which represents 23% of the tested population. An additional 16 other chromosomal abnormalities were identified including trisomy 13, 21, and 22. One patient had abnormal homozygosity. There were multiple duplications and deletions of various chromosomes.

Diagnosis	Number with diagnosis	Number of Tested (%)	Number of patients tested with diagnosis of 22q11 (%)
TOF/PS	126	69 (55%)	11 (16%)
TOF/ absent valve	5	3 (60%)	2 (75%)
IAA Type B	7	6 (86%)	5 (83%)
IAA type A	2	2 (100%)	0 (0)
Truncus	10	8 (80%)	2 (25%)
TOF/ PA	20	16 (80%)	4 (25%)
Total	170	104 (61%)	24 (23%)

Table 1. Demographics of Patients Included in Analysis

Genetics consultation was performed in 79/170 patients (46%). There were 7 patients with TOF/PS and 1 with TA who did not receive genetic testing (Table 2). A pre-operative admission occurred in 102 (60%) of the patients (Table 3). The majority of pre-operative admissions were patients with TOF/PS. All patients with TA had a pre-operative admission. Only one patient out of 20 was not admitted to our institution for pulmonary atresia and multiple aorto-pulmonary collaterals. This patient came from a separate country where she was stabilized as an outpatient prior to referral to our center. Over 75% of our patients who were admitted pre-operatively had genetic testing for 22q11. This compares to 35% of patients tested who were not admitted pre-operatively (Table 3).

With regards to follow up, 51 of the 170 patients were seen in our neurodevelopmental follow up clinic. Only 10 of the 24 patients with 22q11 deletions had documented developmental follow up. An additional 5 patients with other chromosomal abnormalities were seen by our development team. Most patients with neurodevelopmental follow up did not have documented chromosomal abnormalities or their genetics were unknown.

Diagnosis	Number of patients tested for 22q11 deletion	Number of patients with genetics consult	Number of patients with genetics consult who had testing
TOF/PS	69	53 (77%)	46 (67%)
TOF/ absent valve	3	2 (67%)	2 (67%)
IAA Type B	6	5 (83%)	5 (83%)
IAA type A	2	1 (50%)	1 (50%)
Truncus	8	8 (100%)	7 (88%)
TOF/ PA	16	10 (63%)	10 (63%)
Total	104	79 (76%)	71 (68%)

Table 2. Relationship between genetics consultation and testing for 22q11 deletion

Diagnosis	Number of pre-op admits	Number of pre-op admits who had testing
TOF/PS	59	45 (76%)
TOF/ absent valve	5	3 (60%)
IAA Type B	7	6 (86%)
IAA type A	2	2 (100%)
Truncus	10	8 (80%)
TOF/ PA	19	16 (84%)
Total	102	80 (78%)

Table 3. Association between pre-operative admissions and testing for 22q11 deletion

Discussion

This study highlights our institutional deficiency in appropriate genetic testing for all patients with conotruncal abnormalities. We found similar rates of 22q11 deletion by diagnosis compared to previously published reports [3, 5]. Importantly, our study highlights that about 40% of patients have not been tested. Based on prevalence data, this suggests that there is a subset of patients with undiagnosed genetic abnormalities. These are missed opportunities for our patients who are at risk for comorbidities and neurodevelopmental delays.

Because of the importance in counselling families and screening for comorbidities, appropriate genetic screening has been emphasized by the American College of Cardiology (ACC)

and Adult Congenital and Pediatric Cardiology Section's Ambulatory Pediatric Cardiology Quality Metrics Working Group (ACPC) [7] in this patient population. One study published rates for some of the quality metrics endorsed by ACPC, including TOF [8]. Our study examined factors which made genetic testing more likely. A preoperative admission positively correlated with genetic testing completion as well as obtaining a genetics consult. This is likely a result of many standing practices such as admission order sets which prompt genetics consult or genetic testing in sick neonates upon admission.

Most surprising is the low number of neurodevelopmental follow ups. Neurodevelopmental follow up is recommended for all children with congenital heart disease who undergo repair before one year of age because of the associated disorders [9]. A neurodevelopmental evaluation in this small study was only performed in 30% of patients. The population of neurodevelopmental follow up was small making it difficult to assess outcomes. We uncovered a variance in practice for genetic testing and neurodevelopmental follow up in our patient population.

Future Direction

This retrospective review highlights an opportunity for quality improvement processes for our patients. Because of the association of chromosomal abnormalities with our patients with conotruncal defects, we need to standardize our processes for obtaining genetic testing. We saw that genetics consults correlated with genetic testing. Ideally, all testing would be performed and resulted prior to cardiac repair. Developing a fast track to genetics for our patients would be one strategy. Appropriate follow up for patients with neurodevelopment requires standardization. Alternate satellite clinics or "Direct to consumer" virtual visits should be considered to rid the barrier related to travel distance for at risk patients, and we need to better partner with local communities to provide additional resources for our patients. Utilizing telemedicine can augment timely genetic diagnoses and developmental assessments.

Limitations

Our data is limited by several factors. As a referral center covering large distances, we may be missing patients who are seen elsewhere for subspecialty care. Pre-natal genetic testing may have been performed in some patients, but the results were not communicated. Because we have a variety of mechanisms for referral into our surgical program, combined with varying levels of trainees who care for our patients, there may be a lack of knowledge regarding the importance of genetic testing in this specific population. We do not have a designated electronic notification in the charts of the presence of abnormal genetic testing, and it is possible that some patients were tested, but finding the documentation in the medical records was missed. Currently, our neurodevelopmental clinics are available in a limited geographic area. Our patients also come from a large demographic area and patients may be less likely to follow up due to socioeconomic factors. We excluded patients whose follow up was done at other facilities because we wanted to be able to include outpatient data in our assessments. However, this may affect the results related to our inpatient data.

Conclusion

In this single center study, we found our rate of genetic testing in patients with conotruncal abnormalities is low. Recommendation of neurodevelopmental follow up is not systematic for our patients. Future quality improvement initiatives to increase genetic testing and neurodevelopmental follow up are needed.

Conflict of Interest: No funding supported this study. There are no conflicts of interest to report.

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