Pattern of Congenital Heart Defects in 22q11 Microdeletion Syndrome in India – A Tertiary Care Cardiac Hospital Based Study

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Abstract

Background
To investigate pattern of Congenital Heart Defects in 22q11 microdeletion syndrome.

Methods
A retrospective study from year 2006 to 2015 of children with 22q11 microdeletion and pattern of Congenital Heart Defects.

Results
Ninety-Six children with Fluorescent in-situ Hybridisation positive for 22q11.2 microdeletion and Congenital Heart Defects were identified. Out of these 96, the most common Congenital Heart Defect variants were Tetralogy of Fallot (39.58%), Pulmonary Atresia with Ventricular Septal Defect (29.16%), and isolated Ventricular Septal Defect (10.4%). Conotruncal defects constituted majority (82%) followed by Ventricular Septal Defects. Two rare associations were: one child with mitral valve prolapse & another with left pulmonary vein stenosis.

Conclusion
22q11.2 microdeletion syndrome is commonly associated with Congenital Heart Defects. Among children with Congenital Heart Defects and 22q11.2 microdeletion, conotruncal malformations were the most common defects followed by Ventricular Septal Defect.

Keywords: Conotruncal malformations; Tetralogy of Fallot; Pulmonary Atresia with Ventricular Septal Defect

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Introduction

The 22q11.2 microdeletion syndrome is one of the common microdeletion syndromes seen among children with Congenital Heart Defects. Population based studies have shown the prevalence of 22q11.2 microdeletion syndrome range from 1 in 4000 to 1 in 6000 live births.[1,2] Over 80% of children with 22q11.2 microdeletion syndrome have Congenital Heart Defects.[1,3,4] Diagnosis of 22q11.2 microdeletion syndrome among children with Congenital Heart Defects has an implication on medical & surgical management of Congenital Heart Defects. Since more than 30% of these children have associated major extracardiac anomalies (other than velopalatal anomalies) which may present late in life, it becomes important to look for them and follow them up.[1] Thus, 22q11.2 microdeletion syndrome has major implications not only on the health of the affected child but also on the quality of life of other members in the family. The 22q11.2 microdeletion syndrome is characterized by variable clinical features consisting of Congenital Heart Defects, aplasia or hypoplasia of the thymus and/or parathyroid glands, immune functional abnormalities, palatal abnormalities, speech delay, learning difficulties, intellectual disability, facial dysmorphism, hypothyroidism, genitourinary malformations and so on.[1,3,4] Main diagnostic clues to 22q11.2 microdeletion syndrome could be typical Congenital Heart Defects (conotruncal anomalies or aortic arch anomalies), characteristic phenotypic features and other extracardiac manifestations like hypocalcemia.[3,4,5] However clinical features of 22q11.2 microdeletion syndrome are highly variable. Few children might have variable or subtle phenotypic features and might not have typical Congenital Heart Defects.

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Objective of the present study was to describe the pattern of Congenital Heart Defects in children with 22q11.2 microdeletion syndrome in a cohort from a tertiary care cardiac institute in India.

Methods

Study Design and Subject Population

This retrospective study was conducted from January 2006 to February 2015 at Narayana Institute of Cardiac Sciences and Mazumdar Shah Medical Centre, Bangalore, India. Children with Congenital Heart Defects who were also diagnosed positive for 22q11.2 microdeletion were included in the study. The study was based on the data of children who were evaluated at department of Paediatric Cardiology for Congenital Heart Defects. Any child with Congenital Heart Defects with co-existing phenotypic features suggestive of syndromic associations was referred to the department of Medical Genetics, where these children were evaluated by consultant geneticist and investigated further with chromosome analysis and targeted fluorescent in-situ hybridization test using LSI TUPLE1 /ARSA probe from Vysis Inc.,USA for 22q11.2 microdeletion. The study was approved by the institutional review board and clearance from ethical committee was obtained, complying with ethical guidelines of the 1975 Declaration of Helsinki.

Data Retrieval and Evaluation

Cardiac evaluation and echocardiography details of all those children who tested positive for 22q11.2 microdeletion were retrieved from Electronic data records of Narayana Institute of Cardiac Sciences. Details of additional evaluations like cardiac Computerised Tomography and cardiac catheterization were also retrieved whenever done. Complete details of cardiac evaluation were further matched, verified and categorised by Paediatric Cardiologists.

Table 1. Pattern of Congenital Heart Diseases in 22q11.2 microdeletion positive patients

Type of Congenital Heart Defect	No (n=96)	%
Tetralogy of Fallot	38	39.58
Pulmonary atresia with Ventricular septal defect	28	29.16
Ventricular septal defect	10	10.4
Tetralogy of Fallot with Absent pulmonary valve	1	1.04
Interrupted aortic arch	3	3.12
Persistent Truncus Arteriosus	6	6.25
Double outlet right ventricle	3	3.12
Atrial septal defect	4	4.16
Ventricular septal defect with Atrial septal defect	1	1.04
Mitral valve prolapse	1	1.04
Pulmonary vein stenosis	1	1.04
Total	96	100%

Table 2. Conotruncal heart defects

Type of Congenital Heart Defect	No (n=79)	Percent of total number of Conotruncal Defects
Tetralogy of Fallot	38	50.00
Pulmonary atresia with ventricular septal defect	28	36.84
Tetralogy of Fallot with Absent pulmonary valve	1	1.31
Interrupted aortic arch	3	3.94
Persistent Truncus Arteriosus	6	7.89
Double outlet right ventricle	3	3.94
Total	79/96 (82.29%)	

Results

Study Participants and Variants

Overall, 96 children with Congenital Heart Defects with phenotypic features suggestive of 22q11.2 microdeletion syndrome were found to be Fluorescent in-situ Hybridisation positive for 22q11.2 microdeletion. Among the 96 children, 54 were male (56.2%) and 42 were female (43.75%). Out of these 96, the youngest was aged 6 days and the oldest was 32 years old. Totally 93 were less than 18 years old (96.8%). Thirty-four children were less than one year of age at the time of diagnosis (35.4%). All the children had characteristic facial features suggestive of 22q11.2 microdeletion syndrome. The pattern of Congenital Heart Defects seen is listed in Table 1.

Tetralogy of Fallot was the commonest Congenital Heart Defects (n = 38/96, 39.58%). This was followed by Pulmonary Atresia with Ventricular Septal Defect (n = 28/96, 29.16%) and isolated Ventricular Septal Defect (n = 10, 10.4%). Overall, conotruncal defects were documented in 79 out of 96 children (82.29%). All conotruncal defects found in the study are listed in Table 2.

All the 96 children had normal viscerocardial arrangement. There was no incidence of isomerism. Among the 96 children, 95 had levocardia & one had dextrocardia. Right aortic arch was seen in 34 children (35.41%) and the remaining 62 (64.5%) had left aortic arch. Aberrant subclavian artery was seen in 8 (8.4%) and bilateral superior caval veins along with uninterrupted inferior caval vein in 5 (5.2%) children. The aortic arch anomalies, aberrant subclavian artery and bilateral superior caval veins were seen only in association with conotruncal heart defects. These associations are detailed in Table 3.

Tetralogy Of Fallot

Tetralogy of Fallot was most common defect among these 96. It was found in 38 children (39.58%). Fourteen of these children had cardiac Computerised Tomography and 2 underwent cardiac catheterization to delineate anatomical details. Among these 38, right aortic arch was found in 18 children (47.4%). In addition, 5 out of these 38 had aberrant subclavian artery (13.2%) - three in the

Table 3. Congenital heart defects with aortic arch anomalies, aberrant subclavian artery and bilateral superior caval veins

Type of Congenital Heart Defect	Total No	Right sided aortic arch	Aberrant Subclavian artery	Bilateral Superior Caval Veins
Tetralogy of Fallot	38	18	5	3
Pulmonary atresia, with Ventricular Septal Defect	28	10	1	2
Ventricular Septal Defect	10	1	1	-
Tetralogy of Fallot with Absent pulmonary valve	1	1	1	-
Interrupted aortic arch	3	1	-	-
Persistent Truncus Arteriosus	6	2	-	-
Double outlet right ventricle	3	1	-	-
Atrial Septal Defect	4	-	-	-
Ventricular Septal Defect with Atrial Septal Defect	1	-	-	-
Mitral valve prolapse	1	-	-	-
Pulmonary vein stenosis	1	-	-	-
Total	96	34	8	5

right arch subgroup and two in the left aortic arch subgroup. In one child with right aortic arch, the left subclaivan artery was found to be arising from left pulmonary artery. Confluent branch pulmonary arteries were seen in 37 children. In one child, the main pulmonary artery continued as right pulmonary artery with a patent arterial duct continuing as left pulmonary artery. Other associated findings among all children with Tetralogy of Fallot were – Atrial Septal Defects in 12 (31.6%), patent oval foramen in 4 (10.5%), patent arterial duct in 5 (13.2%), bilateral superior caval veins in 3 (7.9%).

Pulmonary Atresia with Ventricular Septal Defect

Pulmonary atresia with Ventricular Septal Defect was the second most common Congenital Heart Defects found in the cohort of 96 children (n = 28/96, 29.16%). Of these, cardiac Computerised Tomography was performed in 10 children and three children underwent cardiac catheterization. Out of the 28, right aortic arch was present in 10 (35.7%). Branch pulmonary arteries were confluent in 15 (53.6%) and non-confluent in 13 (46.4%). Additional Atrial Septal Defect was present in 7 children (25%). Another one child has Atrial Septal Defect with total anomalous pulmonary venous drainage to right atrium. One child had severe stenosis at the origin of right pulmonary artery with arterial collaterals joining at right hilum as detected in cardiac catheterization. Aberrant left subclavian artery was found in one child. One child had severe stenosis of glottis requiring tracheostomy prior to surgery and reconstructive surgery for the airway issue. It was interesting to note that the incidence of right aortic was higher in Tetralogy of Fallot than in Pulmonary Atresia with Ventricular Septal Defect in the cohort of present study.

Ventricular Septal Defect

Total number of children in the series with isolated Ventricular Septal Defect was 10 (10.4%). Out of these, Ventricular Septal Defect was perimembranous in location in 9 (90%), and upper muscular in the other one (10%). One child among these ten had right arch with aberrant left subclavian artery and branch pulmonary arteries arising from different planes, as evidenced in cardiac Computerised Tomography. One more child had Ventricular Septal Defect with an associated moderate Atrial Septal Defect. There were no children with outlet Ventricular Septal Defect in the cohort of present study. In this subset of isolated Ventricular Septal Defect, we have not included other lesions which had Ventricular Septal Defect as a part of their association.

Persistent Truncus Arteriosus

Persistent Truncus Arteriosus was seen in 6 children out of the cohort of 96 (6.25%). All the six children had aortic dominance with closely placed branch pulmonary arteries. Two children among the six had right aortic arch (33.3%) and four had left aortic arch (66.7%). All the six had a large Ventricular Septal Defect underneath the Persistent Truncus Arteriosus. Four among these six (66.7%) had trileaflet valve guarding the Persistent Truncus Arteriosus, one had four-leaflets and one had dysplastic bileaflet valve.

Atrial Septal Defect and interatrial communications

Four children among the 96 had isolated Atrial Septal Defect (4.16%). A small patent arterial duct was also noticed in one among these four. In addition, in one child superior sinus venosus defect (of superior caval venous type) with anomalous drainage of right upper pulmonary vein into right atrium was seen. Also, as described earlier, one more child had Atrial Septal Defect with an associated moderate Ventricular Septal Defect. Atrial Septal Defect found as co-existing lesions with other defects are not included in this subgroup.

Interrupted aortic arch

Interrupted Aortic Arch was noticed in 3 children (3.12%) In one among these three, interruption was distal to the origin of left subclavian artery. In the other two, interruption was just distal to left common carotid artery, with left subclavian artery arising distal to the interrupted segment, with right aortic arch in one of these two. All three children in this group had Ventricular Septal Defect and two had Atrial Septal Defect in addition.

Double outlet right ventricle

Three children were found to have Double Outlet Right Ventricle (3.12%). All three had large Ventricular Septal Defect in outlet region. All three had normal visceroatrial situs, but one had

Table 4. Comparison of percentage of Congenital Heart Defects associations with 22q11microdeletion syndrome in different studies

	Present study 2015	McDonald-McGinn15 1999	Park et al4 2007	Peyvandi et al5 2013	Grassi et al16 2014
n	96	222	190	187	46
TOF (%)	39.58	22	63.2	43.8	38.3
PA-VSD (%)	29.16	-	20.5	15.5	12.7
VSD (%)	10.4	13	5.3	13.4	21.3
PTA (%)	6.25	7	1.7	17.6	8.5
ASD (%)	4.16	3	3.6	-	6.4
IAA (%)	3.12	15	5.3	24	8.5
DORV (%)	3.12	2	3.6	0.5	-

TOF = tetralogy of Fallot, PA = pulmonary atresia, VSD = ventricular septal defect, PTA = persistent truncus arteriosus, ASD = atrial septal defect, IAA = interrupted aortic arch , DORV = double-outlet right ventricle.

dextrocardia. Right aortic arch was found in one child. In another child we noticed aortic valve placed left and anterior to pulmonary valve, which by itself is a rare association. Great arteries in one child were normally related and another had side by side great arteries with aorta to right and pulmonary artery to left.

Other cardiac lesions

Tetralogy with absent pulmonary valve was found in one child (1.04%). This child had right aortic arch with aberrant origin of left subclavian artery. One more child had left pulmonary veins draining into a confluence and draining into left atrium with stenosed opening. This child had intact interatrial septum with no other lesion within the heart. One child had congenital prolapse of mitral valve leaflets without any significant mitral regurgitation. There were no other structural defects in the heart of this child.

Discussion

Congenital Heart Defects are one of the most common human malformations and the most common autosomal microdeletion found in children with Congenital Heart Defects is 22q11.2 microdeletion[2,6] Despite numerous studies on congenital heart diseases with 22q11.2 microdeletion published in last two decades, studies from developing countries are quite few. Being one of the largest centres in the world to treat congenital heart diseases[7], the present study with unique format was designed.

In many studies, children with 22q11.2 microdeletion syndrome were identified and Congenital Heart Defects among them were described.[3,4,8,9] In other studies, children with selected cardiac diagnosis were screened for 22q11.2 microdeletion to identify the relative frequency.[5,10-13] In the present study cardiac diagnosis of all the children with positive for 22q11.2 microdeletion were studied in detail using available data on retrospective basis.

The association of conotruncal defects with 22q11.2 microdeletion syndrome is well established in many studies.[5,11-13] The present study found 82.29% of the cohort with conotruncal defects. This appears to be a common phenomenon in various studies across the world in different geographic zones.[3,4]

Most common Congenital Heart Defects among all 96 children with 22q11.2 microdeletion syndrome was Tetralogy of Fallot (39.58%). This represented 50% of all conotruncal lesions seen in the cohort. This was followed by pulmonary atresia with Ventricular Septal Defect (29.16%) which amounted to 36.84% of all conotruncal lesions. Similar pattern is described by other two studies by Ryan et al and Park et al.[3,4] Prevalence of 22q11.2 microdeletion among conotruncal heart defects range form 13-48%.[5,12,14] Conotruncal defects associated with aortic arch anomalies, aberrant subclavian artery and anomalies of pulmonary artery and pulmonary blood supply, abnormal infundibular septum and abnormal semilunar valves are more likely to be diagnosed with 22q11.2 microdeletion syndrome.[13,14] Incidence of these vascular aberrations in the present study was seen in higher association among conotruncal anomalies. One interesting observation in the present study was the incidence of Right aortic arch which was higher in Tetralogy of Fallot subset than Pulmonary atresia with Ventricular Septal Defect subset.

Isolated Ventricular Septal Defect was found in 10.4% in the present study with another one child presenting with combination of Ventricular Septal Defect and Atrial Septal Defect. Marino et al had pointed out the variations in the location of Ventricular Septal Defect in Asian population as against Caucasian population.[13] A Korean multicentre study by Park et al found isolated Ventricular Septal Defect in 20.5% out of a cohort of 190 children with Congenital Heart Defects and 22q11.2 microdeletion syndrome.[4] These numbers are higher than the 14-18% reported in studies by McDonald-McGinn et al[15] and Ryan et al.[3] Numbers in the present study are consistent with 10% association found in study from McElhinney et al who studied 22q11.2 microdeletion syndrome in children with Ventricular Septal Defect.[10] In the present study, Ventricular Septal Defect was perimembranous in 9 (90% of all isolated Ventricular Septal Defect), and upper muscular in one child (10%). One more child with posterior malaigned Ventricular Septal Defect, had additional Atrial Septal Defect. The distribution is in line with Marino et al[13] who found perimembranous defect in 10 out of 15 children with Ventricular Septal Defect in their cohort. However their study did not have muscular Ventricular Septal Defect. The present study did not have any child with outlet Ventricular Septal Defect among the study cohort.

Persistent Truncus Arteriosus was found in 6.25% of children in the study cohort. This number is significantly more than the 1.7% association found in multicentric Korean study by Park et al[4] but marginally lesser than 8.5% association found in study by Grassi et al.[16]

Amongst all the conotruncal defects, Persistent Truncus Arteriosus constituted 7.89%. This is much lower than the association found in those studies with only conotruncal anomalies with 22q11.2 microdeletion syndrome. The study by Peyvandi et al[5] reported 17.6% Persistent Truncus Arteriosus among all children with conotruncal defects with 22q11.2 microdeletion syndrome.

The present study observed 4.16% association with isolated Atrial Septal Defect. This is consistent with 3.6% association of Park et al but less than 6% found in the series of Grassi et al[16] and more than 3% found in the study cohort of McDonald-McGinn.[15]

One major deviation the present study observed was in the association of Interrupted Aortic Arch, which was only 3.16%. Most of the studies report much higher incidence. McDonald-McGinn et al[15] has reported 15% association, whereas Grassi et al16 showed it to be 8.5% and Park et al4 gave 5.3% association. In study by Peyvandi et al[5] the association was as much as 24%. Double outlet right ventricle was seen in 3.12%. This is consistent with 3.6% association found in Korean Multicentric study by Park et al.[4]

Other lesions in the present study were not in sufficient numbers to draw any comparison with other studies. One child with abnormal pattern of left pulmonary veins and one child with mitral valve prolapse were seen in the present study, which are not reported as standard association with 22q11.2 microdeletion syndrome in earlier studies. Table 4 compares the incidence of different Congenital Heart Defects found in association with 22q11.2 microdeletion syndrome in the present study with few other studies.

The pertinence of diagnosing 22q11.2 microdeletion syndrome in every child undergoing cardiac surgery cannot be overemphasized. It is a well known prognostic indicator. Beyond the cardiac needs, diagnosing 22q11.2 microdeletion syndrome has multiple non-cardiac implications, which were beyond the scope of the present study.

Study Limitations

Not all children with Congenital Heart Defects are seen by consultant geneticist. The genetics referral is decided by Paediatric Cardiologists based on identification of abnormal phenotypic features during out-patient evaluation. Hence, such referrals depend upon the experience of the out-patient consultant. Many children with 22q11.2 microdeletion syndrome might have escaped the diagnosis at Paediatric Cardiac out-patient evaluation due to evolving or lack of strong phenotypic markers. Few children who were advised opinion from geneticist might have refused it for multiple reasons. Many children with Congenital Heart Defects who were advised genetic investigations did not agree to get the test done. In Indian scenario, genetic testing comes with additional cost and has to be borne by parents themselves. This might explain the reluctance of parents for genetic evaluation. Overall, the denominator for the study population could not be defined accurately. Any comparison with other studies thereby becomes difficult.

Due to all these limitations, the cohort in the present study is an insufficient representation of affected population. Since not many such studies have come from Indian sub-continent so far, the present study is an attempt for filling in the void to some extent.

Conclusion

In view of implications involved in long-term management and prognosis of affected children, along with impact on the quality of life amongst family members, all children with Congenital Heart Defects should be evaluated for their genetic basis. However, limitations for diagnosis are multiple. One of the major ways to accomplish the diagnosis is by identifying the high-risk substrate of Congenital Heart Defects population like conotruncal heart defects especially with aortic arch anomalies, aberrant subclavian arteries, bilateral superior caval veins, and interrupted aortic arch. Since the association with Congenital Heart Defects and 22q11.2 microdeletion syndrome is well established, large number of high-risk population can be identified in this subset of children. This can further help in designing adequate cost-benefit model with associated clinical care benefits in managing children with 22q11.2 microdeletion syndrome life-long. The purpose of present study was to achieve the same despite all the limitations the study had to incur. With development of better and cheaper diagnostic modalities, larger studies with better design and higher numbers are to be expected in future.

Declarations of Interest

The authors declare no conflicts of interest.

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Ethical Standards:

The authors assert that all procedures contributing to the work comply with the ethical standards of the relevant guidelines on human experimentation. The study was approved by the Ethics Committee of Narayana Health City, Bangalore, India. (NHH/MEC-CL-2015-329, dated 25th June 2015).

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