ORIGINAL ARTICLE

Congenital Heart Defects Associated with Atrial Heterotaxy

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ABSTRACT

Objective: To determine the frequency of various congenital cardiac defects associated with atrial heterotaxy and the difference between spectrum of cardiac defects in right atrial isomerism (RAI) and left atrial isomerism (LAI) in these patients.

Study Design: Cross-sectional observational study.

Place and Duration of Study: Department of Cardiology, The Children's Hospital and Institute of Child Health, Lahore, from July 2006 to June 2011.

Methodology: All children presenting to the hospital with suspected congenital heart defect were included in the study. Echocardiography based sequential segmental analysis was used, taking atrial symmetry, interrupted inferior vena cava (IVC) and juxtaposed aorta to IVC relation into account for identifying atrial heterotaxy. Various segmental defects were noted for RAI and LAI.

Results: Children had atrial heterotaxy (M:F; 1.7:1) with 61.6% (n=82) having LAI. Most common lesions associated with RAI included complete atrioventricular (AV) septal defect (n=48, 94.1%), single AV valve (n=45, 88.2%) and pulmonary outflow tract obstruction (n=41, 80.4%). LAI was associated with ventricular septal defect (n=68, 82.9%), atrial septal defect (n=63, 76.8%, mostly secundum variety), and miscellaneous left sided obstructive lesions.

Conclusion: Atrial heterotaxy encompasses a wide spectrum of congenital cardiac defects. The frequency of various defects associated with RAI or LAI in local South Asian population of Lahore, Pakistan is similar to those as reported in the Western literature.

Key words: *Atrial heterotaxy. Congenital heart defect. Segmental sequential analysis. children.*

INTRODUCTION

Atrial heterotaxy is a defect of cardiac lateralization resulting in symmetrical development of both atria rather than normal asymmetrical configuration.[1] This defect in lateralization is not confined to atria but involves other parts of heart as well as configuration of various abdomino-thoracic viscera. The exact cause of atrial heterotaxy remains elusive though several genes have been reported to effect sidedness of cardiac structures. *Pitx2, Lefty, Cited2, Sonic Hedgehog* and *Horizon III* genes have been implicated.[2,3] Careful genetic studies, however, support multifactorial nature of underlying pathology.[4]

The term atrial heterotaxy includes right atrial isomerism (RAI) and left atrial isomerism (LAI) sometimes collectively labelled as situs ambiguous. It is still unclear whether both these entities are distinct abnormalities or the ends of the spectrum of the same defect. Cardiac anomalies associated with RAI and LAI overlap a great deal. However, certain differences exist in distribution of segmental anomalies of the heart. Moreover, abdominal visceral situs does not follow the atrial situs strictly.[5] Atrial heterotaxy is also associated with immune deficiency syndromes due to ineffective splenic function. Long-term outcome is often poor due to overwhelming infection. The structural differences have shown variation among various ethnic and regional groups. A few East Asian studies have shown much higher incidence of RAI than LAI when compared with the western literature along with variations in associated cardiac defects.[6,7]

Segmental sequential analysis used for systematic evaluation of congenital cardiac defect on the basis of echocardiographic study, provides a valuable insight into individual segmental arrangement and anomalies associated with atrial heterotaxy.[8]

In this study, the aim was to determine the distribution of cardiac lesions in patients with atrial heterotaxy presenting to tertiary care centre, Lahore, Pakistan by analyzing the frequency of atrial heterotaxy and evaluating the differences in associated cardiac anomalies between LAI and RAI conditions.

METHODOLOGY

This cross-sectional study was conducted at the Department of Paediatric Cardiology and Cardiac Surgery, The Children's Hospital and Institute of Child Health, Lahore, Pakistan. All children presenting to the department with suspicion of congenital cardiac defect

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on the basis of clinical examination, ECG and chest radiograph were evaluated from July 2006 to June 2011 following an informed consent from the parents. Those found to have atrial heterotaxy were finally evaluated. As no intervention was involved and investigations were according to institutional guidelines, ethical approval was not sought. The demographic profile and age at presentation were recorded. Chest radiograph and electrocardiogram were obtained in all children prior to echocardiography as per departmental protocol. Echocardiography was performed by two experienced consultant paediatric cardiologists [Authors 2, 3] and repeated by a senior consultant [Author 4], if there was some ambiguity in initial study. Atrial heterotaxy was labelled when both the atria showed similar morphology instead of usual asymmetry. LAI and RAI were differentiated on the basis of atrial appendage morphology supported by juxtaposed position of abdominal aorta and inferior vena cava, bilateral hyparterial bronchi on chest radiograph or abnormal P-wave vector (LAI) on ECG, where evident.[1] Segmental sequential analysis was performed and all the segmental arrangements and defects were recorded.

The data was entered and analyzed through Statistical Package for Social Sciences (SPSS) version 17. Frequencies and percentages were calculated for qualitative variables including gender, type of isomerism and all segmental variables. Mean value and standard deviation was calculated for quantitative data including age. Independant t-test was used to find any significant difference in age of various subgroups after confirming normal distribution. Chi-square test was used as test of significance, taking p-value < 0.05 as significant while comparing gender, age and various segmental anomalies in patients with LAI and RAI.

RESULTS

The age of the patients ranged from newborns till 16 years. Congenital heart disease (CHD) was detected in 12,375 patients. Atrial heterotaxy was detected in 133 patients (1.1% of all CHD). Mean age of presentation was 23.3 $\pm$ 41.9 months (95% C.I: 16.1 - 31.4 months). LAI was much more common (n = 82, 61.7%) in patients with atrial heterotaxy than RAI (n = 51, 38.3%). Atrial heterotaxy was more common in boys (n = 83) than girls (n = 50, M:F=1.7:1). There was no significant difference in gender distribution between patients with LAI and RAI, (p = 0.76). Patients with RAI presented at a slightly younger age (19.6 $\pm$ 40.0 months; 95% C.I.: 8.1 - 31.1 months) than those with LAI (25.6 $\pm$ 42.4 months; 95% C.I.: 16.3 - 34.9 months). Age at presentation was significantly lower in children having RAI with unrestricted pulmonary flow (4.4 $\pm$ 5.6 months) than children with LAI (32.2 $\pm$ 48.4 months, p = 0.003).

Table I shows frequency of various congenital heart defects detected in children with atrial heterotaxy. Interrupted suprarenal IVC was not detected in any patient with RAI (p = 0.004, Table II). RAI was associated with significantly higher frequency of primum atrial septal defect (ASD) or common atrium (n = 48/51, 94.1%, p = 0.009). ASDs were of secundum variety in

Table I: Frequency of various cardiac defects in patients with atrial heterotaxy on segmental sequential analysis.

Cardiac defect	Number of Patients (n) (N=133)	Frequency (%)
Dextrocardia/mesocardia	40	30.1%
LAI	82	61.7%
Interrupted IVC	12	9.0%
Bilateral SVC	06	4.5%
Cardiac / infracardiac TAPVC	06	4.5%
Atrial septal defect	111	83.5%
Ventricular septal defect	118	88.7%
Unbalanced ventricles/univentricular heart	63	47.4%
Right sided / undetermined morphology of dominant ventricle in univentricular hearts (n=63)	46	73.0%
Single atrioventricular valve	88	66.2%
Two separate components in single atrioventricular valve hearts (n=88)	83	94.3%
Left AV valve regurgitation	34	26.8%
Discordant ventriculoarterial connection	68	51.1%
Stenotic or atretic pulmonary valve	97	72.9%
Non-confluent branch pulmonary arteries	04	3.0%
Right aortic arch	23	17.3%
Hypoplasia, coarctation or interruption aortic arch	03	2.2%

Legends: *IVC = Inferior vena cava; SVC = Superior vena cava; TAPVC = Total anomalous pulmonary venous connections; AV = Atrioventricular valve.*

Table II: Comparison of frequency of cardiac defects in LAI and RAI on segmental sequential analysis..

Cardiac defect	LAI [n (%)] (N=82)	RAI [n (%)] (N=51)	p value
Dextrocardia/mesocardia	26 (31.7%)	14 (27.4%)	0.6
Interrupted IVC	12 (14.6)	0 (0.0%)	0.004
Bilateral SVC	05 (6.1%)	01 (2.0%)	0.26
Cardiac / infracardiac TAPVC	03 (3.6%)	03 (5.9%)	0.55
Atrial septal defect	63 (76.8%)	48 (94.1%)	0.009
Ventricular septal defect	68 (82.9%)	50 (98.0%)	0.007
Unbalanced Ventricles	35 (42.7%)	28 (54.9%)	0.17
Right sided / undetermined morphology of dominant ventricle	24/33 (72.7%)	22/27 (81.5%)	0.43
Single atrioventricular valve	43 (52.4%)	45 (88.2%)	< 0.001
Two separate components of single atrioventricular valve	40/43 (93.0%)	43/45 (95.6%)	0.61
Left AV valve regurgitation	20 (24.4%)	14 (27.5%)	0.88
Discordant ventriculoarterial connection	37 (45.1%)	36 (70.6%)	0.004
Stenotic or atretic pulmonary valve	49 (59.8%)	41 (80.4%)	0.013
Non-confluent branch pulmonary arteries	01 (1.2%)	02 (3.9%)	0.31
Right aortic arch	16 (19.5%)	07 (13.7%)	0.39
Hypoplasia, coarctation or interruption aortic arch	03 (3.6%)	0 (0.0%)	0.17
Patent arterial duct	32 (39.0%)	21 (41.2%)	0.81

Legends: *IVC = Inferior vena cava; SVC = Superior vena cava; TAPVC = Total anomalous pulmonary venous connections; AV = Atrioventricular valve.*

LAI in contrast to primum ASDs in RAI. Inlet type ventricular septal defect (VSD) was common in both forms of atrial heterotaxy, however, significantly higher in RAI (RAI 98%, n = 50, vs. LAI 82.9%, n = 68, p = 0.007). Various other striking differences in the distribution of congenital defect between LAI and RAI are presented in Table II. Right sided obstructive lesions including pulmonary stenosis or pulmonary atresia, though present in both forms of atrial heterotaxy, were significantly more common in RAI (41/51, 80.4% vs. 49/82, 59.7%, p=0.01). LAI was associated with higher frequency of left sided obstructed lesions compared to RAI including mitral atresia (n = 04), coarctation of aorta (n = 03), hypoplastic left heart syndrome (n = 02), cor triatriatum (n = 02), interrupted aortic arch (n = 01), hypoplastic aortic arch (n = 01) and valvular aortic stenosis (n = 01).

DISCUSSION

Atrial heterotaxy was found to be 1.1% of all CHDs presenting to our tertiary care centre. The frequencies have been documented as high as 1.7 - 2.8%.[9,10] LAI (61.6%) was much more common than RAI. Most Western and Far Eastern studies showed a similar frequency of LAI in patients with atrial heterotaxy.[11-16] A few studies from Taiwan and Singapore reported much higher frequency of RAI.[6,7] LAI is usually associated with less severe cardiac defects and can occur in isolation. LAI may not come into notice until being screened for visceral abnormalities. There was no regional difference in our population when compared with Western literature.

Interrupted suprarenal IVC was only found in patients with LAI. It was in accordance with previous studies.[13,14] Interrupted IVC can be the only abnormal finding associated with LAI. Interrupted suprarenal IVC has been reported as extremely rare in association with RAI.[10] SVC arrangement was not significantly associated with any typical form of heterotaxy. Supracardiac TAPVC was not found in any patient. In most children, the TAPVC was cardiac with pulmonary veins opening directly into RA. It was mostly due to malaligned interatrial septum. This finding was in contrast with previous literature, where extracardiac TAPVC and obstructed pulmonary veins were frequently associated with atrial heterotaxy.[10,12]

Interatrial septum was defective or absent in almost all cases with RAI. Majority of ASDs associated with LAI were secundum ASD in contrast to primum ASDs in RAI.[17] This supports the recent evidence showing interatrial septum as a left sided structure rather than a midline structure as previously believed.[18] Ventricular septal defect was common in both form of atrial heterotaxy. This defect was significantly more common with RAI (98.0%). Ventricles were unbalanced in almost half of the patients with atrial heterotaxy; 54.9% in RAI and 42.7% in LAI. Abnormal endocardial cushion development or abnormal looping of the cardiac tube has been postulated. Seventy three percent of these had right ventricular morphology, more in cases with RAI (81.5%). Right ventricular morphology in univentricular heart is associated with poor post-surgical outcome.[19] Right ventricle is not able to support systemic circulation and this results in heart failure in the long-run. The papillary muscles have been found to be hypoplastic, disproportional, or even absent in right isomerism than in hearts with normal atrial arrangement. LAI also had tendencies but not as prominent.[20,21] Single AV valve was also significantly associated with RAI (88.2%). Left AV valve insufficiency was found in 34 (26.8%). Insufficiency of the left atrioventricular valve was found to be much higher in previous studies (63.6%).[22] It may be due to younger age group of children in this study. Left AV valve insufficiency has also been associated with poor surgical outcome.[19]

RAI mostly presented with right sided obstructed lesions. Complete atrioventricular septal defect (CAVSD), double outlet right ventricle (DORV), transposition of great arteries (TGA) with pulmonary stenosis (PS) or pulmonary atresia (PA) were the most common lesions in patients with RAI. This finding was in accordance with previous studies showing high frequency of CAVSD, TGA, PS or PA associated with RAI.[11] LAI was associated with low but significant frequency of left sided obstructive lesions along with hypoplastic left heart syndrome. Similar finding have been reported previously with LAI.[23] Left sided obstructive lesions, though less frequent in atrial heterotaxy, are associated with poor outcome.[23]

Very few patients underwent surgical procedures, cardiac catheterization or autopsy. Hence confirmation of the echocardiographic findings was not possible through direct observation. However, echocardiography could demonstrate clearly isomeric atrial morphology in all these children. The visceroatrial concordance was not studied as the aim was to focus on cardiac defects associated with atrial heterotaxy using segmental sequential analysis. The long-term outcome and surgical results were not evaluated in this study. However, many factors other than wide spectrum of cardiac defects affect the final prognosis. Associated abdominal visceral abnormalities, cardiac arrhythmias and immune deficiency are among the most important factors determining the surgical outcome.

CONCLUSION

Atrial heterotaxy is associated with a wide range of cardiac defects involving all segments of the heart. There is a fair degree of overlap between defects associated with right and left atrial isomerism. The data shows similarities with the spectrum of congenital heart

defect reported in Western population emphasize the involvement of genetic mutations rather than regional or environmental variation resulting in defects of lateralization and associated cardiac defects.

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