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## Research Article

### Heterotaxy Syndrome and Atrial Isomerism in Fetal Life: Spectrum of Anomalies and Potential Antenatal Diagnostic Markers

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#### ABSTRACT

Heterotaxy [HTX] is an abnormal arrangement of organs across the left-right axis of the body. It is associated with complex cardiac malformations and altered extra-cardiac anatomy. Many a times, the classical patterns are not found, thus posing problems in diagnosis of the condition.

Atrial isomerism is a major component of HTX. It is also associated with significant morbidity and mortality. So, early prenatal diagnosis of HTX is important as it can help to make plans for proper surgical management of cardiac problems after birth. This can help to improve the survival outcome.

Obstruction to pulmonary outflow, total anomalous pulmonary venous connection (TAPVC), partial anomalous pulmonary venous connection (PAPVC), double outlet right ventricle (DORV) and viscerocardiac heterotaxy

(VCH) are seen in both the isomerisms, hence any two of these conditions when seen should arouse high suspicion to diagnose HTX isomerism. Right atrial isomerism (RAI) being associated with complex cardiac defects, its diagnosis is a difficult task. But extracardiac features like juxtaposition of inferior vena cava (IVC) with aorta and presence of asplenia can be used as the markers to confirm RAI. Similarly, one of the extracardiac components like an interrupted IVC with azygous continuation or polysplenia along with cardiac components like bradyarrhythmias or heartblocks should suffice to label the condition as left atrial isomerism (LAI). A stepwise logical analysis if planned can help to assess and describe HTX adequately on antenatal scans.

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## INTRODUCTION

Heterotaxy is an abnormality where internal thoraco-abdominal organs demonstrate abnormal arrangement across left-right axis of body<sup>1</sup>. Atrial isomerism is a major component of heterotaxy. It is associated with significant morbidity and mortality. Incidence of HTX is as high as 1:10,000 live-births<sup>2</sup>. Interestingly, Asians show a higher prevalence of heterotaxy syndrome (32%) compared to Westerners<sup>3</sup>. The male: female ratio is 2:1<sup>4</sup>. Heterotaxy accounts for around 3% of cases of congenital heart diseases worldwide<sup>5</sup>. The heterotaxy syndrome is typically associated with complex cardiovascular malformations. The proper description of heart in patients with this syndrome needs a complete description of arrangement of atrial appendages, ventricular topology, position of heart in chest, veno-atrial connections etc<sup>6</sup>. Alterations in extracardiac anatomy help to diagnose the condition, but many a times some cases do not follow classical pattern causing diagnostic problems.

### Aims and Objectives:

- 1) To explain cardiac and extra-cardiac components of the syndrome.
- 2) To identify various markers of Heterotaxy syndrome to ease the approach antenatally.
- 3) To highlight how each case of Heterotaxy syndrome can be unique and the classic patterns are breached.

### METHODOLOGY:

We had come across two cases of HTX in GMC, Gondia. The findings obtained from these cases of HTX reported in our institute were analyzed along with the data obtained from the comprehensive overview of literature collected after an extensive literature search.

*Inclusion criteria:* The studies or cases where HTX was detected antenatally and confirmed postnatally during autopsy or on postmortem were included.

*Exclusion criteria:* The studies where even though antenatal detection was done but postnatal detection or autopsy was not done for HTX features were excluded. As the data was of qualitative nature and moreover it belonged to

varying circumstances at time points, the quantitative analysis were not possible but simple descriptive measure like frequency and percentages were used to summarize the study parameters. The data was tabulated and analyzed to find out the conditions that were repeatedly seen in left and right atrial isomerism respectively.

**Period of Study:** January 2019 to December 2020

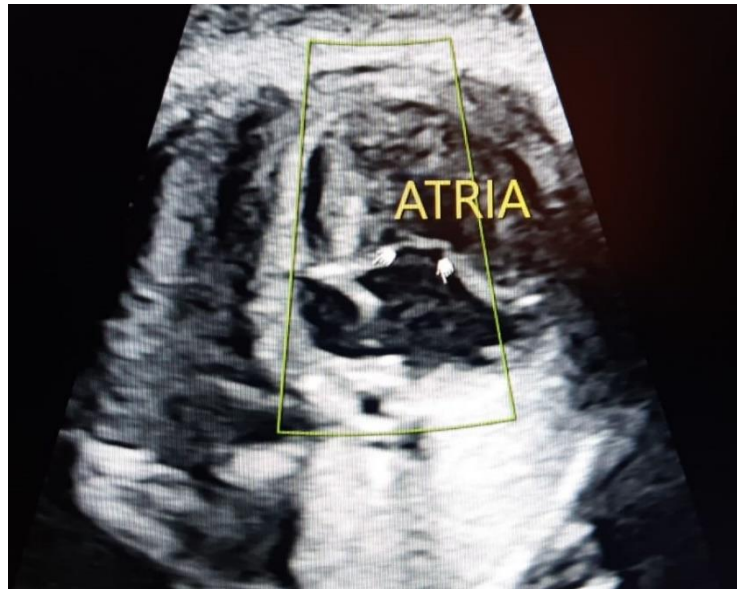
**Place of Study:** Govt. Medical College, Gondia, Maharashtra.

### RESULTS:

Case 1: A 23 year old primigravida had shown on ultrasound, a single live intrauterine fetus of 33 weeks, 6 days with mild oligohydramnios, complex cardiac anomaly (monoventricular cavity with large AVSD with both atria of left atrial morphology i.e. left atrial isomerism (Figure1), single AV valve, and single outflow tract arising from right ventricle which appears to be morphological left ventricle) and central liver as a part of extra-cardiac anomaly of HTX. Case 2: Another antenatally detected case of HTX was reported in the same period in our institute which was also evaluated on the basis of the documented evidence generated from the overview. She was a young second gravida female who was diagnosed with heterotaxy syndrome at 33 weeks. The cardiac anomalies detected were, a large AV septal defect, bilateral atria of left atrial morphology (Figure 2) & right ventricular dilatation. Aortic stenosis with bicuspid aortic valve and distal aortic dilatation, ductus arteriosus shows normal flow. The extracardiac anomalies found were LVOT formed by aorta with overriding, liver is central and spleen & stomach are on right side (Figure 3a), suprarenal IVC is absent with azygous continuation of IVC (Figure 3b) with bradycardia (Figure 4). Features were suggestive of heterotaxy with left atrial isomerism. FHR was lower side of normal during her antenatal period. She finally underwent an LSCS for persistent bradycardia, which was in range of 80 to 100 FHR/min. On investigations after birth: Antenatal USG

findings were verified. ECHO showed situs ambiguous levocardia, AV-VA concordance, common atria with absent interatrial septum, dilated right ventricle, interrupted IVC. Pulmonary veins were forming a common chamber behind LA draining into coronary

sinus. Large inlet VSD with bidirectional shunt (Figure 5), small PDA with bidirectional shunt, severe pulmonary artery hypertension/dilated main pulmonary artery, mixed (left pulmonary vein drains to LV and right pulmonary veins to the coronary sinus) TAPVC (Figure6).

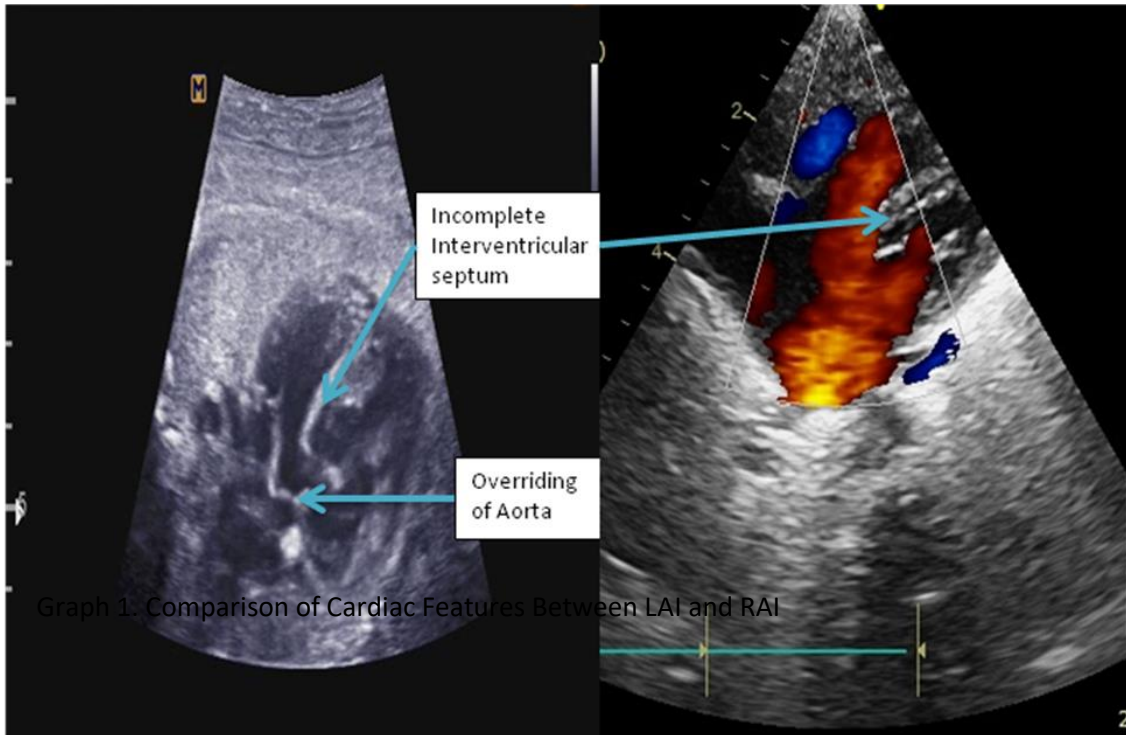


*Figure 1. AVSD with Left Atrial Isomerism (Case 1)*



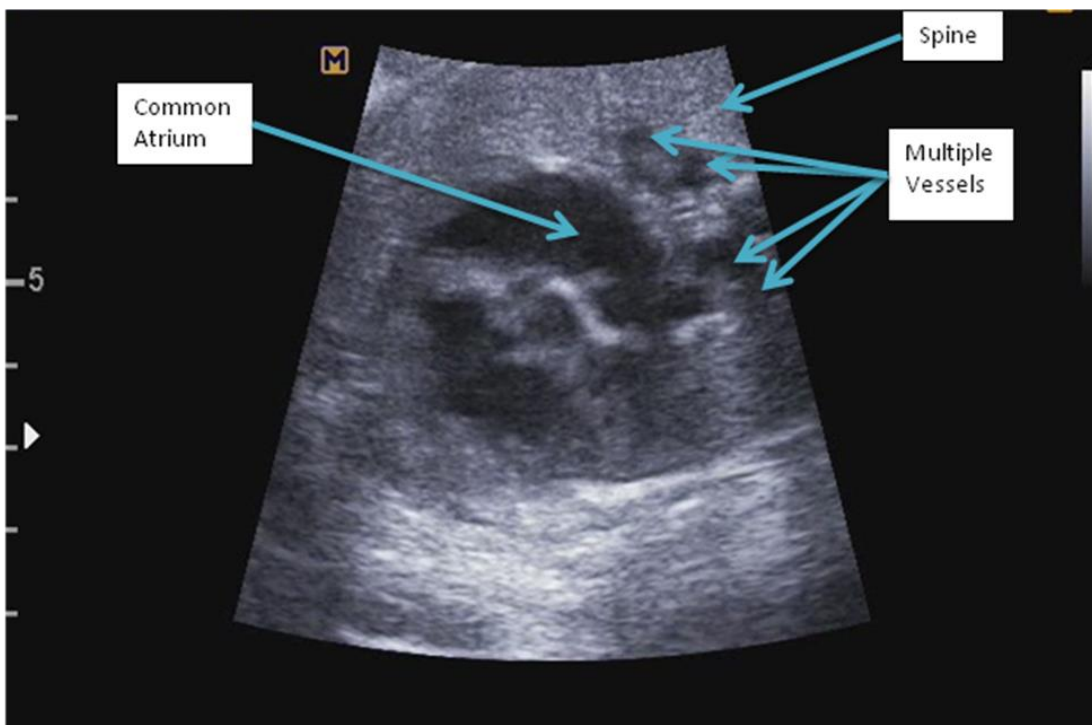
*Figure 2 LAI showing both Appendages with Left Atrial Morphology (Case 2)*



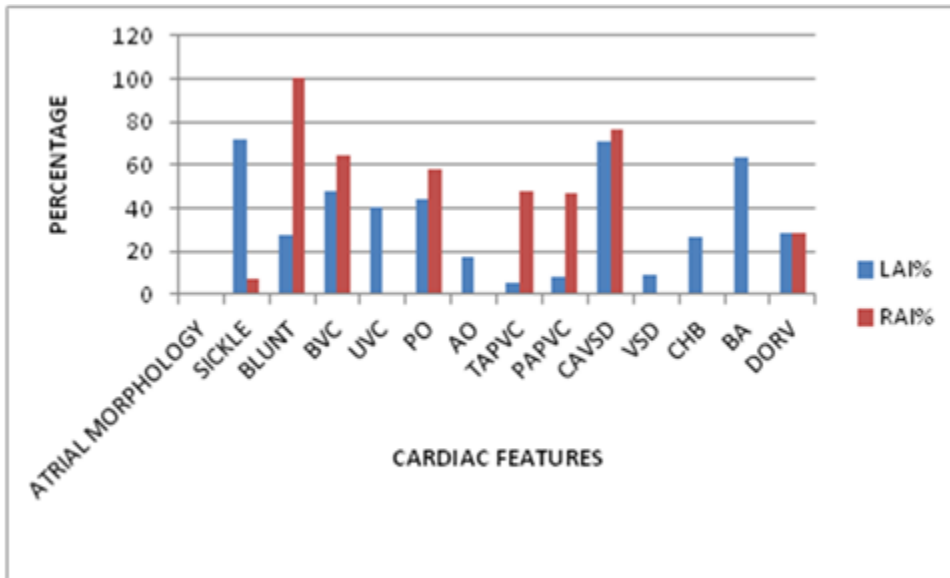


Graph 1. Comparison of Cardiac Features Between LAI and RAI

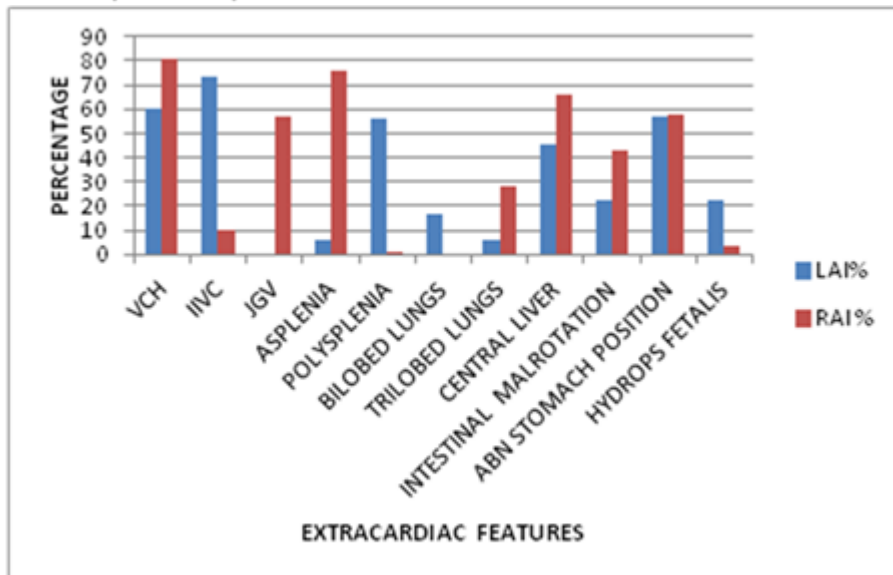
*Figure 5 Incomplete Interventricular Septum showing bidirectional flow on Doppler with Overriding of Aorta*



*Figure 6 Multiple Vessels between common Atrium and Spine suggesting Mixed TAPVC*



Graph 1. Comparison of Cardiac Features Between LAI and RAI



Graph 2. Comparison of Extra-Cardiac Features Between LAI and RAI

*Table 2. Comparison of Cardiac Features Between LAI and RA*

Cardiac		LAI	RAI
Atrial Isomerism	Sickle	72.22	7.0
	Blunt	27.77	100
Biventricular AV connection		47.6	64.3
Univentricular AV connection		40	0
AV Septal defect		70.56	76
VSD		9.41	0
DORV		28	28.78
Heart Block		26.47	0
Bradyarrhythmia		63.85	0
TAPVC		5.27	47.58
PAPVC		7.77	47.2

*Table 3. Comparison of Extra-Cardiac Features Between LAI and RAI*

Extra-cardiac	LAI	RAI
Obstruction to pulmonary flow	44.2	58.3
Obstruction to Aortic flow	17.33	0
Interruption of IVC	73.7	10
VCH	60	80.7
Juxtaposition of great vessels	0	57
Asplenia/Hyposplenia	6.19	76.09
Polysplenia	56.12	1.25
Bilobed Lung	16.66	0
Trilobed Lung	5.55	28.5
Central Liver	45.2	65.7
Intestinal malrotation	22.16	43.12
Abnormal Stomach position	56.9	57.8
Hydrops fetalis	22.6	3.33

Thus, our patient with LAI had left atrial morphology (sickle shaped), biventricular AV connections, CAVSD, Obstruction to aortic flow, bradyarrhythmias and mixed TAPVC as cardiac findings. VCH, Interrupted IVC with azygous continuation and ambiguous position of spleen and stomach bubble were seen as extra-cardiac findings. Case 1: The baby

expired within 3 days of birth, but postmortem was not conducted. Hence this patient could not satisfy the inclusion criteria of the study and was excluded.

Case 2: Data from this interesting case from the institute was collated with the data gathered from the literature. The extensive search led to 5<sup>7-11</sup> studies which satisfied the specified

criteria. These results were compiled tabulated and analyzed as follows:

**CARDIAC COMPONENTS:** Table 2, Graph 1

**ATRIAL MORPHOLOGY:** The atrial morphology with sickle shaped appendages is common with LAI 72.22 %, while the blunt shaped morphology is common with the RAI 100%. Very few studies have shown a variation from this classic pattern.

**Ventricular Connections:** As seen from the table biventricular connections (64.28%) are more common with RAI, while uni-ventricular connections (40%) appear to be an important feature in LAI. Pulmonary outflow obstruction is found to be an important component of both the HTX syndrome and isomerism, but aortic outflow obstruction is specifically seen with LAI.

**TAPVC/PAPVC (47.58% /14.28%)** is an important feature of the HTX syndrome and is more often associated with RAI. Isolated ASD and VSD are the commonly seen congenital heart defects. But here we see that Combined AVSD (CAVSD) is seen in both types of isomerisms, so when CAVSD is detected antenatally it can arouse suspicion of isomerisms.

In LAI 63.85% had Bradycardia and 26.47% had Heart Blocks, while none had it in RAI. This means that brady-arrhythmias and heart blocks are an exclusive feature of LAI alone. DORV (28%) commonly seen in both types of atrial isomerisms, is also an important component of HTX syndrome.

**EXTRACARDIAC:** As seen from the Table. No 3 and Graph 2 (Bar diagram). VCH is common with HTX Syndrome (LAI 60%; RAI 80.70%). Juxtaposition of great vessels seems an exclusive feature of RAI (57% IN RAI Vs 0% IN LAI). The graph here also shows that, Interrupted IVC is seen in 73.70 % in LAI as against a meager 10% in RAI. This suggests that Interrupted IVC can prove to be an important feature for LAI, whereas

juxtaposition of great vessels is for RAI, if detected in antenatal scans.

Asplenia (76.09%) is common in RAI while polysplenia (56.12%) is seen more with LAI. The percentage of cases seen (LAI 45.28%./RAI 65.78%) suggest that a centrally located liver is an important feature in both isomerisms and is equally important component of VCH. Thus it can be an important countenance to suspect HTX antenatally.

Abnormal stomach position is almost equally seen in both the isomerisms (56.92% in LAI vs 57.89% in RAI). Percentage of Intestinal malrotation is relatively more in RAI (43.12% in RAI Vs 22.16% in LAI) although it is detected in LAI too. Although rare, the % of hydrops appears to be significantly high in LAI (22.60% in LAI Vs 3.33% in RAI)

While LAI are more associated with bilobed lungs (16.66% in LAI Vs 0% in RAI), the trilobed lungs (28.57% in RAI Vs 5.55% in LAI) are commonly seen in RAI.

Bilobed and trilobed lungs were additional findings on imaging by MRI or, autopsy or on postmortem in the fetuses that were antenatally diagnosed as having HTX.

**DISCUSSION:** Heterotaxy is an abnormal arrangement of viscera across the left-right axis of the body. Situs amibiguus is defined as an abnormality in which there are components of situs solitus (normal arrangement) and situs inversus (mirror imaged arrangement) in the same person. Situs ambiguous therefore can be considered to be present when the thoracic and abdominal organs are positioned in such a way with respect to each other as to be not clearly lateralized, thus having neither the normal nor the mirror image arrangements.

This study discusses the historical racial and ethnical aspect of HTX (Table 1) and also highlights the various cardiac and extracardiac components of HTX while identifying the markers.

*Table 1: Historical aspect of Isomerism: (Cezary: Diagnostic problems in fetal vhs)<sup>12</sup>*

	Ivemark (1955) <sup>12</sup>	First to describe asplenia
	Van Mierop and Winglesworth(1962) <sup>12</sup>	Cardiac and extracardiac association of partial situs inversus with splenic anomalies
	Anderson and Becker(1976) <sup>12</sup>	Morphology of atrial appendages but not entire atrium is relevant
	Van Praagh(1990) <sup>12</sup>	Denied the concept of asplenia and polysplenia syndrome and denied the value of atrial situs evaluation
	Siew Yen Ho et al(1991) <sup>7</sup>	All hearts with isomerism of right atrial appendage have bilateral sinus node and those with left isomerism showed absence of a recognizable sinus node
	Uemura (1995) <sup>30</sup>	Correlation of atrial morphology with other cardiac defects
	C. Berg et al(2005) <sup>11</sup>	In fetal echo study found all left isomerism cases with bilateral sickle shaped atrial morphology and all right isomerism cases with bilateral blunt shape atrial morphology
	Cezary et al(2012) <sup>12</sup>	Characteristic features of left and right isomerisms may be present in various forms and some cases do not follow classical patterns creating diagnostic problems
	Lili Huang et al (2015) <sup>17</sup>	Heterotaxy subdivided into right and left isomerism according to its blood supply; the one broad based, receiving blood from IVC being right atrium and the smaller narrower one receiving blood from pulmonary veins being left atrium.
	Yim et al(2018) <sup>1</sup>	Right or left isomerism determined by shape of appendage and extent of pectinate muscles

**Racial & Ethnical aspects:**

HTX has widely divergent population based estimates of prevalence, racial and ethnic predominance and mortality in current literature. Lopez et al (2015)<sup>13</sup> stated that the rates of HTX are higher among Hispanic infants of Mexican origin. There was a twofold higher female preponderance for infants of mothers who were non Hispanic white or black. Mothers with diabetes were three times more likely to have a child with HTX compared with non diabetics. In India no racial studies and no studies related to association with diabetes mellitus either has been observed so far in the literature.

LAI occurs in <1% children with congenital heart disease and occurs more frequently in females.<sup>14</sup> Certain factors like diabetes mellitus, smoking, exposure to hair dyes, cocaine and certain lab chemicals can affect a woman during pregnancy and may also contribute to the risk of Heterotaxy syndrome in her child.<sup>15</sup>

The appearance of signs and symptoms would largely depend on presence or absence of association with cardiac and extracardiac defects. **Appendages:** In Isomerism the paired structures on opposite sides in the human body are in morphological terms symmetrical mirror images of each other. Thus right or left isomerism is

defined by the arrangement of the atrial appendages.

**Markers Defined for LAI and RAI:**

**Atrio-Ventricular connections:** David W. Sapire MD et al<sup>16</sup> studied 51 patients of atrial isomerisms and stated that an ambiguous and biventricular connection was the commonest type of atrio-ventricular connection in left isomerism. Common AV valve is the frequent mode of connection in both isomerisms.

**Pulmonary/ Aortic outflow obstruction:**

**DORV:** Cezary Niszczota (2012)<sup>12</sup> states that the conotruncal anomalies (DORV, TGA, TOF, pulmonary stenosis or atresia etc) are not usually seen in association with AVSD. When both are seen together heterotaxy syndrome should be suspected. Conotruncal anomalies like aortic stenosis, mixed TAPVC, PDA in association with large inlet VSD and small ostium secundum ASD was seen in our hospital case. **TAPVC/PAPVC:** **Huang Lili et al (2019) states that** total TAPVC is common in both forms of isomerism<sup>17</sup>. Susan Foerster<sup>18</sup> et al (2008) explained that in modern surgical era the mortality remains high among patients of heterotaxy with obstructed TAPVC. Pulmonary vein stenosis is also associated with poor outcomes. This therefore explains the importance of TAPVC. In our patient the mixed TAPVC with right sided pulmonary veins draining into right atrium and left sided pulmonary veins forming a common chamber behind left atrium draining into coronary sinus were seen along with constriction at the base of the aorta (instead of pulmonary).

**CAVSD:** Yim et al(2018)<sup>1</sup> in his study of disharmonious patterns of heterotaxy and isomerism found an association of classic left isomerism with AVSD in 68%, atrial and ventricular septal defect in 22%, hypoplastic left heart syndrome in 9% along with concordant ventriculo-arterial connection in 59% and aortic stenosis or atresia in 19%. In the present study also Combined AVSD was a remarkable feature detected antenatally in both the isomerisms. Thus, CAVSD can be a marker to provoke one for evaluating further on grounds of HTX.

**Heart Block and Bradyarrhythmias:** According to Yim et al<sup>1</sup>, arrhythmias predominantly complete heart blocks were more common in patients with

left isomerism (27%) than with right isomerism (6%).

In the present study the baby had constriction at the base of aorta along with antenatal bradycardia and postnatally also the heart rate was in a lower range. Bradyarrhythmias and Heart Block: In study by Wu MH et al (2001)<sup>19</sup>, the patients with LAI had a high probability of developing bradyarrhythmias due to abnormal sinus node function

Momma K et al (1990)<sup>20</sup> stated that multiplicity and progressive slowing of atrial rhythm are characteristic in patients with left isomerism. Siew Yen Ho et al (1991)<sup>7</sup> mentioned that the cases with isomerism of left appendages showed absence of recognizable sinus node except in 4 cases in which a small remnant of node was found. They explained that the sinus node is an excellent histological marker of the morphological right appendage. Thus absence or hypoplastic sinus node explains the heart blocks or slower heart rate in LAI and arrhythmias in RAI. C.Berg<sup>9</sup> (2005) in his study on AV block also described that a low atrial rate was significantly associated with LAI which matches the results of Schmidt et al (1991)<sup>21</sup>. Thus bradyarrhythmias and heart blocks are an exclusive feature of LAI. If both Interrupted IVC and complete heart block are observed, we can almost be sure that there is LAI as stated differently by J H Lin(2002)<sup>22</sup>, S Meryl (2006)<sup>23</sup>, S Swaminathan (2007)<sup>24</sup>.

**Extracardiac:**

**Interrupted IVC and Azygous connection:**

Colin K et al (1996)<sup>25</sup> in their study 'Left atrial isomerism detected in fetal life' reviewed 10 cases at their centre. Postnatal imaging and autopsies provided definitive diagnosis. Echo markers included large azygous continuation of an Interrupted IVC, AV block with structural heart disease and viscerocardiac heterotaxy. They also found that the incidence of AV septal defect and pulmonary outflow obstruction in live births were 50% and 45% respectively; while they were found much more frequently among stillbirths (80% each). Soo Jin Kim<sup>3</sup> observed the presence of isomerism of left atrial appendages with interrupted inferior caval vein.

Our patient with LAI also showed interrupted IVC with azygous vein continuation along with

bradycardia and VCH. Table 3 shows that, there is a strong association of LAI with bradyarrhythmias and interrupted IVC with Azygous continuation. So these two conditions can be considered as markers for HTX with LAI. Interrupted IVC is an important feature which is seen sonologically in antenatal period only, later it needs a more costly and complicated investigation like MRI to detect it in postnatal life, as food particles can obscure the waves and thus fail to give a clear image of the condition. Huang Lili et al<sup>12</sup> typical left isomerism is characterized by bilateral morphological left pulmonary arteries, IVC interruption at suprarenal level with continuation as azygous or hemiazygous to the SVC. Yim et al<sup>1</sup> found interrupted IVC in 78 % of classic left isomerism and no cases of right isomerism.

According to study by Bartz et al (2006)<sup>26</sup>, heterotaxy includes ambiguous abdominal situs (76%), asplenia (54%), polysplenia (46%), TAPVC 64%, interruption of IVC with Azygous continuation 54%, in a total of 142 patients with HTX syndrome.

**Juxtaposition of great vessels:** Dilli A et al (2012)<sup>27</sup> in his case report on LAI has found right sided aortic arch with left sided IVC ( Juxtaposition) and a right sided cardiac apex with a dominant liver. Small and large intestines also had some degree of malrotation.

**Asplenia and Polysplenia:** Polysplenia is common in left isomerism and in female subjects, while intestinal malrotation occurs in both with a higher incidence in right isomerism.<sup>17</sup> Maria C et al (2014)<sup>28</sup> studied 154 fetuses with Heterotaxy where 93 had polysplenia with bradyarrhythmias and 61 had asplenia with pulmonary vein stenosis. A study by Cezary Niszczota et al (2012)<sup>12</sup> was done to determine whether the classical features can be helpful or misleading in visceral heterotaxy syndrome. They found none of the fetuses with LAI presented 'polysplenia' and none of the fetuses with RAI presented with 'asplenia'. Over the years the patients collected in the groups of heterotaxy syndrome have been described in terms of 'asplenia' or 'polysplenia' J P Jacobs, R H Anderson (2011)<sup>6</sup>, U Bartram (2005)<sup>29</sup>. According to Uemura's (1995)<sup>30</sup> study, the diagnosis of VHS (Visceral Heterotaxy

Syndrome) should be based mostly on morphology of the atriums (like tubular appendage having a narrow junction with the rest of the atrium). Maria C<sup>28</sup> in NIH have differentiated HTX on the basis of asplenia and polysplenia and later evaluated them for features of HTX syndrome antenatally as well as postnatally. Thus, various studies are done to classify HTX based on certain features but such classic patterns are not always seen thereby creating problem in diagnosis and differentiation.

**VCH:**

**Centrally placed Liver, Abnormal Stomach position, Intestinal Malrotation:**

D.S.Carneiro et al<sup>4</sup> in 2013 presented a case of heterotaxy syndrome with LAI, dextrocardia, interruption of IVC, AV septal defect, polysplenia, bilobed lungs, hyparterial bronchus and centrally located liver. Soo Jin Kim (2006)<sup>3</sup> in a review article of HTX mentioned that diagnosis of LAI is associated with two-thirds having simpler or milder forms of range of cardiac diseases. Hence to diagnose as left isomerism, it becomes necessary to evaluate for extracardiac anomalies like bilobed lungs with long bronchus, polysplenia, biliary atresia, intestinal malrotation, central liver. In right isomerism, the patients frequently have trilobed lungs with short bronchus and asplenia. Jeremy Grubin et al (2015)<sup>31</sup> in a case review of heterotaxy syndrome with polysplenia found a midline liver with a more prominent left lobe, stomach was right sided with multiple right sided spleens, bilobed lungs, hyparterial bronchus, and interrupted IVC with azygous continuation along with left atrial isomerism .

Soo Jin Kim et al<sup>3</sup> in their study of HTX has found the presence of isomerism of left atrial appendages in association with interrupted IVC and no other cardiac or vascular abnormalities. According to them such patients may never be diagnosed as having isomerism unless extracardiac anomalies such as biliary atresia or intestinal malrotation drew attention to the abnormal arrangement of the abdominal organs.

In our hospital case left isomerism was not associated with polysplenia, but spleen and stomach were placed on right side but without intestinal malrotation. Thus, once again though

classic patterns are not found, but visualization of midline or central liver is an important feature of VCH. Intestinal malrotation can draw attention to diagnose by looking for cardiac anomalies or mirror images of appendages carefully.

**Hydrops fetalis:** In a study 'Outcome of prenatally diagnosed fetal heterotaxy: systemic review and meta-analysis' by Buca et al(2018)<sup>32</sup>, it was mentioned that hydrops developed in approximately 10% of fetuses affected by LAI, mainly because of the presence of complete AV block, which occurs in a quarter of cases.

**Bilobed/ Trilobed Lungs:** Bilobed or trilobed lung is an invariable finding detected by imaging, postnatally or postmortem in cases suspected as having an htx syndrome. It is a difficult feature to be seen or commented upon with an ultrasound which remains as the main safe and cheapest form of investigation antenatally.

Carneiro et al<sup>4</sup> and Kimberly et al (1999)<sup>33</sup> all mentioned that classic LAI or bilateral left sidedness implies the presence of bilobed lungs, central liver, polysplenia, stomach in indeterminate position, IVC interruption.

Yim and Jeremy et al<sup>31</sup> has added to the above features, the presence of hyparterial bronchus in bilobed lung and eparterial bronchus in trilobed lung.

According to Huang Lili<sup>17</sup> left isomerism is associated with bilobed lungs with hyparterial bronchi, **Carneiro DS et al<sup>4</sup>** has also observed a similar spectrum in left isomerism.

Jacobs et al<sup>6</sup> in 2017 in his study on nomenclature of heterotaxy syndrome found RAI to be associated with trilobed lungs and LAI to be associated with bilobed lungs. Further they state that the disharmonious structures should be described separately with atrial appendages, lungs, spleen, etc.

**Ciliary dyskinesia:** At least 12% of people with primary ciliary dyskinesia have heterotaxy syndrome. It appears that cilia play a critical role in establishing left-right asymmetry before birth<sup>15</sup>.

The multiplicity and diversity of findings in heterotaxy syndrome make the individualization of cases extremely valuable as most of them do not perfectly fit in any classification. Thus the

radiological evaluation is indispensable for the identification and planning of approach to patients so as to allow evaluation for alterations in each patient.

### **Embryology, Inheritance pattern and Genetic basis:**

Heterotaxy syndrome accounts for approximately 3 % of all congenital heart defects, more common in Asian populations. Most often, it is sporadic meaning that only one person in a family is affected, however about 10% of patients have a close relative with congenital heart defect. It has a variable expressivity<sup>15</sup>.

According to Dilli A et al<sup>27</sup>, asymmetric or unilateral organs develop from defects in lateralization while viscerovascular regulation seems to occur sporadically.

There seems to be no single etiological factor responsible for the development of abnormal lateralization and isomerism. Evidence from human studies and animal models suggest causal heterogeneity<sup>3</sup>.

**Heterotaxy syndrome** can be caused by mutations in many different genes (at least 20 genes identified). The proteins produced from most of these genes play roles in determining which structures should be on the right side of the body and which should be on the left, a process known as left-right asymmetry. This process occurs during the earliest stages of embryonic development. Rarely, chromosomal changes such as inversions, deletions, duplications and other rearrangements of genetic material have been associated with this condition<sup>15</sup>.

Although some of the situs ambiguous cases are sporadic, autosomal dominant and autosomal recessive hereditary patterns and X-linked inheritance patterns have also been described<sup>28</sup>. X-linked inheritance mode may help in part to explain the male preponderance of this syndrome<sup>34</sup>. Today genetic research supports mostly a multifactorial hereditary model<sup>28</sup>.

In a study by Marja W Wessels et al<sup>35</sup>, a three generation family with 9 patients affected by a combination of cardiac anomalies and left isomerism. The syndrome was inherited as autosomal dominant pattern with suggestive linkage to chromosome 6p.

Genes and chromosomal locations included in VHS (visceral htx) include ZIC3 (Xq26), CFC1 (2q21), ACVR2B(3p21.3-p22), LEFTYA(1q42.1) respectively<sup>32</sup>. Thus, the possibility to assess human genetic predisposition for VHS is increasing rapidly.

#### **Prognosis:**

Maria C et al<sup>28</sup> had concluded that bradyarrhythmias for polysplenia and pulmonary vein stenosis for asplenia are the only predictors/risk factors of post neonatal death.

David W. Sapire et al<sup>16</sup> studied 51 patients and stated that left isomerism is associated with longer survival, its constellation of associated malformation being less severe and more amenable to corrective surgery.

Nevertheless, according to Cezary Niszczota<sup>12</sup>, third degree heart block may cause acute heart failure, fetal hydrops or intrauterine death in LAI. According to literature, complete heart block can be observed in 15-50% cases of LAI.

Buca et al<sup>32</sup>, states that fetal hydrops is one of the major determinants of poor perinatal outcome in fetuses with LAI and can be evident from the first trimester of pregnancy.

Without corrective surgery, most children with HTX and significant heart problems will not survive beyond the first year of life.

Frogoudoki A et al (2003)<sup>36</sup> mentioned that adults with LAI benefit from pacemaker implanted to reduce recurrence of Supraventricular tachycardia and maintain AV synchrony

A study by Children's hospital of Philadelphia<sup>37</sup>, mentions that nearly all patients with RAI require a series of major heart surgeries to establish Fontan circulation.

As per Yim et al<sup>1</sup>, mortality continues to be high although aggressive total anomalous pulmonary venous drainage repair for RAI has been done. The role of sutureless repair for TAPVC drainage remains to be defined.

Without surgical palliation, 95% patients with asplenia and 60% patients with polysplenia will not survive past the first year of life. Lifespan and development vary widely based on surgical outcomes and presence or absence of other co-morbidities<sup>30</sup>.

So, prognosis is difficult to determine due to varying degree of heart defects. Although with

recent advances in medical technology, survival rates have increased significantly.

But, patients with HTX require series of surgeries in neonatal period. The procedures are diverse and reflect the highly variable anatomy of this syndrome. The surgical data suggests an overall poor prognosis for infants with isomerism.

#### **Limitations:**

As the study is a retrospective collection of the qualitative data and a comparison of different literature studies along with an isolated single live case, hence statistical analysis could not be applied here to generalize the results to groups and subgroups of these patient populations. However the study findings highlighted some useful cardiac and extracardiac components associated with HTX and to identify the markers. But the cardiac and extracardiac components associated and markers to be seen are the most useful tools identified here, while antenatally diagnosing a case of HTX.

#### **Scope for future research:**

Literature scan shows very few studies from India. Poor reporting may be one of the reasons for this. No racial studies of heterotaxy syndrome have been done till now, although India has a vast, diverse racial and ethnic background.

There are very few studies showing relation of HTX associated with diabetes mellitus. This aspect needs to be evaluated in view of increasing diabetic population now-a-days. Lopez KN et al<sup>13</sup> in their study 'Racial Disparities in Heterotaxy Syndrome' mentioned that mothers with diabetes mellitus were found to be three times more likely to have a child with HTX compared to non-diabetics (PR=3.13, 95% confidence interval 2.12-4.45). Among non-diabetics, HTX cases were 86% more likely to have a Hispanic mother and 72% a non-Hispanic black mother.

A multi-centric single study plan can give uniformity in collection of the data so as to help for proper application of statistics and evaluation of the markers.

#### **Impression:**

HTX seems a constellation of abnormal findings whereby a single description is not possible. Antenatal diagnosis of the case is valuable but

rarely seen. At the same time, recent advances in medical management especially improvements in cardiac surgical skills and techniques are likely to result in improving the survival of these patients. It has been observed that it is easier to diagnose LAI rather than RAI. LAI can be recognized in cases with an interrupted IVC with azygous continuation and complete heart block.

Prenatal diagnosis of right atrial isomerism remains a difficult task. Important sonographic markers are VCH, complex cardiac malformations, juxtaposition of inferior vena cava and aorta. CAVSD was significantly correlated with non-survival.

Hence there is importance of identifying various components of the condition and its diagnostic markers, because some conditions are related to poor survival.

The cardiac components identified for LAI are univentricular connections, obstruction to aortic flow, heart blocks or bradyarrhythmias. The extracardiac components for LAI are interrupted IVC and polysplenia.

The RAI components noted are juxtaposition of great vessels or a deviation of aorta from the midline along with asplenia. RAI is associated with complex cardiac abnormalities; hence there is difficulty in diagnosis of this condition.

While prenatal diagnosis of left and right isomerism has traditionally relied on the presence of heart block, cardiac defects, interruption of IVC, juxtaposition of IVC and aorta but postnatal diagnostic criteria includes features that are not reliably assessed in-utero (lung lobulation, bronchial branching pattern, splenic status, intestinal malrotations etc.

Colin K et al in their study have sought markers of LAI as interrupted IVC connected to azygous along with structural heart disease (VSD, ASD, TAPVC), bradyarrhythmias, and viscerocardiac heterotaxy. As per him at least one of the markers was seen in all the cases.

The present study brings together the features from various studies so as to identify some most common of them which can be called as markers to help diagnose this complex condition early in prenatal life. It still remains a great challenge in live patients despite using best available diagnostic modalities.

The characteristics like an obstruction to pulmonary outflow, TAPVC/PAPVC, CAVSD, DORV, and VCH are seen often in both the isomerisms, so presence of these conditions can arouse high suspicions regarding isomerism which should then be probed for further so as to come to a precise conclusion regarding the type of isomerism.

Interrupted IVC, heart blocks or bradyarrhythmias, univentricular connections, obstruction to aortic outflow and hydrops are conditions associated with LAI. Any three of these features together may indicate about the fact of dealing with a case of isomerism.

Multiple or complex cardiac defects along with juxtaposition of great vessels can suggest an RAI. Leaving apart the exceptions to the common patterns a stepwise logical analysis can help to assess and describe HTX antenatally adequately and correctly.

#### **Suggested Diagnostic evaluation for HTX:**

The structures to be evaluated with imaging in determining situs are:

- (1) Morphology of atria
- (2) Structural defects (ASD, VSD, CAVSD) and atrioventricular connections of heart
- (3) Ventricular outflow defects (AS, PS, Constriction at base of Aorta)
- (4) Antenatal bradyarrhythmias and heart blocks
- (5) Position of cardiac apex
- (6) Following the IVC for interruption and connection with the Azygous/Hemiazygous
- (7) Position of aorta relative to midline/Juxtaposition with IVC
- (8) Position of stomach
- (9) Malrotation of stomach/intestines
- (10) Position of liver
- (11) Position and number of spleens
- (12) Bilobed or trilobed lungs
- (13) NIHF (Non Immune Hydrops Fetalis)

Diagnostic ability on postmortem or autopsy specimens is certainly high but apt and timely done investigation using proper imaging techniques antenatally can go a long way to improve the patient's outcome.

Appropriate imaging modalities must be precisely used to evaluate the spectrum of abnormality associated with HTX, in order to allow

appropriate counseling of parents and to plan delivery and neonatal management. Being aware of such abnormalities prior to surgery can largely help to use remarkably the advances in surgical techniques. Further, the multiplicity and diversity of findings makes the individualization of cases extremely valuable for proper management. In HTX, the overall prognosis for infants with isomerism, when evaluated from the time of birth remains a greatest challenge for pediatric cardiologists and congenital cardiovascular surgeons.

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