Pre natal evaluation of heterotaxy syndrome by fetal echocardiography and correlating with autopsy

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Abstract

Introduction: Heterotaxy syndrome/ isomerism is characterized by an abnormal symmetry of the viscera that are normally dissimilar due to abnormal lateralization of thoracic and abdominal viscera and is frequently associated with complex cardiac anomalies. Isomerism may be of right or left.

Materials and methods: This article describes the morphological characteristics of heterotaxy and suggests an approach in evaluating the spectrum of abnormalities associated with this syndrome. This study is based on 12 cases diagnosed on antenatal ultrasound as heterotaxy syndrome. Results of the examinations were re-evaluated and compared by fetal autopsy.

Result: Based on the following echocardiographic criteria, a diagnosis of left isomerism was made if there was viscerocardiac heterotaxy associated with an interruption of inferior vena cava or with bilateral finger-like atrial appendages or if it was associated with heart block. If there was evidence of viscerocardiac heterotaxy with complex cardiac anomalies then it was diagnosed as right atrial isomerism or visceral heterotaxy syndrome. We diagnosed 6/12 as left isomerism and rest of the cases as right isomerism/visceral heterotaxy syndrome. In Autopsy we evaluated visceral situs and morphology of the lungs and the main bronchi, the state of the liver, spleen, bowel, and the precise anatomy of the heart and confirmed 4/12 as left isomerism 4/12 as right isomerism and two cases as visceral heterotaxy syndrome (VHS). Rest of the two cases were included in the study despite missing autopsy data, as the combination of abnormal situs with interrupted inferior vena cava, and cardiac malformation allowed a diagnosis of left isomerism with high probability.

Conclusion: In this study, we aimed to find common features of heterotaxy syndrome on prenatal ultrasound as well as on fetal autopsy. This syndrome should be accurately diagnosed in the prenatal period in order to allow appropriate counseling of parents.

Keywords

Fetus, heterotaxy syndrome, echocardiography, autopsy

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Introduction

Heterotaxy: “heteros” means different, “taxis” means arrangement (from the Greek). The internal thoracic organs and the abdominal organs exhibit abnormal left–right relations in heterotaxy syndrome.

Heterotaxy syndrome affects up to one in 10,000 live births and is associated with high mortality rates and is slightly more prevalent in male, at a ratio of 2:1.¹ There may be levocardia, dextrocardia, or mesocardia. Left isomerism is usually associated with polysplenia.

Right isomerism is usually associated with asplenia (Ivermark syndrome).²

Isomerism: “isos” means equal, “meros” means part (from the Greek). Isomerism refers to the similarity of

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bilateral structures that are normally dissimilar. Right isomerism: bilateral structures with morphologic right characteristics, such as bilateral right atria, atrial appendages exhibiting right morphologic features, bilateral eparterial bronchi, and trilobed lungs (Figure 1(a)). In right atrial isomerism (RAI), there is no left atrium to receive pulmonary venous drainage, and total anomalous pulmonary venous drainage into a systemic vein is seen in >50% of cases. Cardiac defects in right isomerism may include transposition of the great arteries, common atrioventricular (AV) valve, ventricular hypoplasia or single ventricle physiology, pulmonary atresia and pulmonary vein obstruction. Right atrial isomerism is usually associated with severe cyanotic heart disease in infancy. Death in the first year of life is common in right isomerism, especially if there are pulmonary atresia and anomalous pulmonary venous return.³

Left isomerism: bilateral left sidedness with maldevelopment of right-side structures. Morphologic left characteristics such as bilateral left bronchi, bilobed lungs, finger-like atrial appendages and an absent or atretic sinoatrial node (Figure 1(b)). In left isomerism, there is often polysplenia. The most common associated cardiovascular anomalies in left isomerism are noncyanotic congenital heart defects including an atrial septal defect, endocardial cushion defects, partial anomalous pulmonary venous return, and up to 50% of cases are associated with dextrocardia.⁴ The most diagnostically useful clinical feature is inferior vena caval (IVC) interruption with azygous continuation, in which the hepatic segment of the inferior cava is absent, and the distal segment continues with the azygos or hemiazygos vein. This is due to failure to form right sub cardinal hepatic anastomosis which results in an absent hepatic segment

of IVC. The sinus node is usually absent bilaterally in left isomerism which may lead to fetal complete heart block. The prognosis of left isomerism may be quite good in the absence of heart block, as it tends to present with less severe cardiac anomalies or even with normal intracardiac anatomy.³ Visceral anomalies like malrotation and malfixation of the bowel, preduodenal portal vein, gastric volvulus, esophageal hiatal hernia, and biliary atresia are common in both left and right isomerism, with a predominance in left isomerism which may strongly affect the long-term outcome of these patients.^{4,5}

Fetal echocardiography is a reliable technique for prenatal diagnosis of cardiac defects as early as 16 weeks gestation.⁶⁻⁹ Prenatal diagnosis based upon the configuration of the atrial appendages has been reported.

Based on different constellations of cardiac and extracardiac findings associated with the left and RAI can be inferred in utero.

Materials and methods

In this cohort study, we prospectively entered the data of 1210 pregnant women referred for routine antenatal scans at Vinoothna sono scan center and Mahatma Gandhi memorial hospital in Warangal, from January 2012 to December 2017. Twelve patients were diagnosed as heterotaxy syndrome. Two-dimensional echo cardiac images were obtained in short and long axis, four chamber and arch views. Pulse wave Doppler, color Doppler mapping, and M-mode were also performed in all studies. Ethical committee approval was taken to conduct the study. Written informed consent was obtained from patients who participated in this study. All studies were performed on voluson E8 and Esoate Mylab 40 using 2–5 MHz transabdominal transducer to

Figure 1. (a) Right atrial isomerism showing bilateral trilobed lung, pyramidal shaped atrial appendages, midline liver and asplenia. (b) Left atrial isomerism showing bilateral bilobed lung, sickle shaped atrial appendages, midline liver and polysplenia.

obtain maximum resolution depending upon maternal habitus and gestational age. In all studies, we attempted to determine the visceral situs, cardiac apex orientation, and atrial morphology. Continuity of IVC was assessed. The segmental approach of the cardia and the area behind the heart was evaluated. An autopsy was performed according to the guidelines of sequential segmental analysis of the heart.^{10–12} All the examinations consisted of two main parts: general evaluation of visceral situs and morphology of the lungs and the main bronchi, the state of liver and spleen, and precise anatomy of the heart (Figure 2). Results of the ultrasound and post-mortem examinations were re-evaluated and compared.

Results

Of 1210 fetal echocardiograms performed, 97 revealed structural heart disease (8%); in those cases, 12 were diagnosed with heterotaxy syndrome (12%). These were categorized based on the following echocardiographic criteria: a diagnosis of left isomerism was made if there was viserocardiac heterotaxy associated with interruption

of IVC, finger-like atrial appendages or if there was heart block (Figures 3–5). If there was evidence of viscerocardiac heterotaxy without the above findings, a diagnosis of RAI/visceral heterotaxy syndrome (VHS) was made (Figures 6 and 7). Prognosis explained, eight out of 12 patients were not willing to continue their pregnancies and opted for termination. Two of them wanted to continue the pregnancy but due to other medical complications pregnancy was terminated (cases 6 and 10; Table 1). Rest of the two cases (cases 11 and 12; Table 1) were included in the study despite missing autopsy data, as the combination of abnormal situs, complex cardiac malformation, and interrupted IVC with prominent azygos vein allowed a diagnosis of left isomerism with high probability. Some of the structural abnormalities can be recognized only during autopsy. The diagnostic criteria of heterotaxy on autopsy include the isomerism of the pulmonary lobes and the bronchial branching (Figure 2(a),(b)). Autopsy confirmed four out of 10 fetuses having RAI (Figure 2(a),(c)). Four were confirmed as left atrial isomerism (LAI; Figure 2(b),(d)) and two cases were diagnosed as VHS (Figure 8(c)). Cardiovascular anomalies comprised: complete

Figure 2. Autopsy findings in isomerism. (a) Autopsy of 20 weeks fetus showing trilobed left lung. (b) Autopsy of 19 weeks fetus showing bilobed right lung with bridging liver and malrotated bowel loops. (c) Autopsy of 21 weeks showing bilateral blunt and pyramidal shaped atrial appendages (AA) with a common arterial trunk (CAT). Cardiac apex left side and stomach (St) on right side. Small arrow indicates CAT, long arrow indicates stomach, arrowhead-St. (d) Levocardia with stomach on rightside.

Figure 3. Left isomerism. (a) Bilateral sickle shaped atrial appendages with atrioventricular septal defect (AVSD). Arrow indicates atrial appendages. (b) total anomalous pulmonary venous connection (TAPVC)-straight vein noted. (c) Transposition of great arteries. (d) Heart block. AO: aorta; AZ: azygos vein; MPA: main pulmonary artery.

Figure 4. Left isomerism. (a) Bilateral sickle shaped atrial appendages with atrioventricular septal defect (AVSD) and azygos vein (AZ). (b) Absent intrahepatic portion of inferior vena cava (IVC) (interrupted IVC). (c) Single outflow tract of truncus arteriosus. (d) Transverse section of abdomen shows azygos vein and aorta (AO) are side by side. CAT: common arterial trunk.

Figure 5. Lt isomerism. (a) Stomach (Stom) is on left side with prominent azygos vein (AZ). (b) Dextrocardia with prominent azygos vein. (c) Parallel course of azygos vein and aorta (AO). (d) Azygos vein entering into superior vena cava (SVC) [azygos arch].

atrioventricular septal defect (cAVSD; Figure 7(a); 9/12), ventriculo-arterial discordance (1/12; Figure 3(c)), truncus arteriosus (3/12; Figure 4(c)), double outlet right ventricle (DORV; 2/12; Figure 6(c)), and tetralogy of Fallot (ToF; 1/12; Figure 7(b)). Pulmonary stenosis (1/12), abnormal systemic venous connections (8/12; Figure 9), partial anomalous pulmonary venous drainage (PAPVD; 1/12), complete anomalous pulmonary venous drainage (3/12; Figure 6(d), 3(b)), persistent left SVC (3/12; Figure 7(c)), dextrocardia in (5/12; Figure 5(b)) mesocardia (3/12). The extracardiac findings are stomach on the right side and central in 6/12 cases (Figure 6(b)). Truncated pancreas in 3/12 cases. Asplenia in 1/12 cases absent gall bladder in 2/12 cases. Interrupted IVC with a continuation of azygos vein in 6/12 cases (Figure 4(b); Tables 1 and 2).

Discussion

There are four embryonic stages where left-right axis might be influenced: (1) breaking of left-right symmetry at early embryogenesis, (2) transmission of asymmetric signals from the node to the lateral plate mesoderm,

(3) asymmetric gene expression in the left lateral plate mesoderm, and (4) left-right asymmetric morphogenesis of the internal organs. In the event that an adjustment happens at the early underlying phases of embryogenesis, there is generally entire reversal of the left-right axis (situs inversus), while hindrance at a later stage may result in just a few organs being influenced, with a randomized position of organs along the left-right axis (heterotaxy) and identical representation and duplication of organs (isomerism).¹³

In 1955, Ivemark first published a study describing asplenia syndrome as “teratologic syndrome of visceral symmetry” associated with cono-truncal anomalies.² In 1962, Van Mierop and Wiglesworth proved that not only severe cardiac malformations exist with splenic anomalies, but also atypical lobation of lungs, state of liver and partial situs inversus may also be observed.¹⁴ Anderson and co-workers suggested that the morphology of atrial appendages, but not entire atrium is relevant.^{15,16} The Uemura’s study correlated morphology of atrial appendages with other cardiac defects characteristic of isomeric left and isomeric right atrial appendages, confirming Anderson’s concept.^{17,18}

Figure 6. Right isomerism. (a) Bilateral blunt pyramidal shaped atrial morphology. (b) Juxta position of descending aorta (ao) and inferior vena cava (IVC). IVC and aorta on right side. Stomach (STO) is nearer to midline. (c) Double outlet right ventricle (RV). (d) Infracardiac total anomalous pulmonary venous drainage. DORV: double outlet right ventricle; LA: left atrium; LV: left ventricle; MPA: main pulmonary artery.

Thus, the nomenclature of VHS was established basing on the morphology of atrial appendages.¹⁹ Morphological features of left atrium are: small finger-like appendage having a narrow communication with rest of the atrium and a smooth surface of the pulmonary venous component. Morphological features of right atrium are: triangular appendage having a broad junction with the venous component of an atrium, distinguished rough pectinate muscle within the appendage, and also extending into the posterior wall of the atrium attaching to the terminal crest (Figure 10). In a normally functioning heart, the right atrium receives blood from below by inferior vena cavae that flows within the right atrial appendage, thereby distending it and forming triangular and huge appendage. This blood flows through the foramen ovale into the left atrium and flows behind the left atrial appendage through mitral valve resulting in the finger-like narrow left appendage.^{20,21} In right isomerism, for most of the time IVC is not interrupted and it is associated with the atrial septal defect. Consequently,

the blood coming from IVC enters into both the appendages distending them and forming bilateral broad appendages (Figures 6(a) and 8(a)). Left isomerism usually associated with interrupted IVC resulting in a reduction of blood flow into the right atrium from below and increased flow from above through superior vena cava which flows through atrioventricular valve directly resulting in bilateral narrow finger-like appendages (Figures 8(b), 3(a), 4(a)).²²

However, some of the cases that do not follow the classical patterns described, may cause diagnostic problems on prenatal as well as on post-mortem examination. In our experience two cases were noted. As we can observe in this study it is easier to diagnose LAI rather than RAI. As per literature and in our observation it is confirmed that the state of the spleen could not divide the overall group of heterotaxy into right and left isomerism, it is only helpful but not crucial in diagnosis. Many investigators reveal that there are some evident features of left and RAI, which are likely to be used in ultrasound. A diagnosis of left isomerism should be

Figure 7. Right isomerism. (a) Atrioventricular septal defect (AVSD). (b) Tetralogy of Fallot. (c) Three vessel trachea view showing persistent left superior vena cava (SVC). (d) Juxta position of descending aorta (AO) and inferior vena cava (IVC). IVC, aorta and stomach (ST) is on left side with persistent right umbilical vein.

strongly suggested in the presence of a combination of at least two of the following: (1) cAVSD or other structural heart disease; (2) interruption of IVC with azygos continuation; (3) early fetal heart block; (4) viscerocardiac heterotaxy. Right isomerism should be suspected in the presence of a combination of at least two of the following: (1) structural heart disease, namely cAVSD; (2) juxtaposition of IVC and descending aorta; (3) viscerocardiac heterotaxy.⁵ If both interrupted IVC and complete heart block are observed, we can almost be sure that there is LAI.^{23,24} In the longitudinal view, the azygos vein and aorta are seen side by side in the same plane. In these cases, color Doppler can be helpful to visualize the flow in both vessels in opposite direction (Figure 6). According to literature, complete heart block can be observed in 15–50% cases of LAI.²⁵ In our study, one case of LAI is associated with complete heart block and Lt isomerism was significantly correlated with an interrupted IVC ($p < 0.025$) and heart block ($p < 0.01$) while right isomerism was significantly correlated with juxtaposition of IVC and aorta

($p > 0.025$) and total anomalous pulmonary venous drainage ($p < 0.05$).

Nonappearance of the coronary sinus and two-sided superior vena cava may be noted in some of the RAI cases.²⁹ Total anomalous pulmonary venous drainage is more commonly observed in RAI than LAI. The conotruncal anomalies (DORV, transposition of the great arteries (TGA), ToF, pulmonary stenosis or atresia and so on) are not as a rule found in a relationship with AVSD.^{26,27} At the point when both are seen together, heterotaxy disorder ought to be suspected. Even our study confirmed the same observation.

VHS might be caused by transformations in qualities that control early left-right axis. Genes implicated in VHS include ZIC3, LEFTYA, CRYPTIC, and ACVR2B.^{28,29} Likewise portrayed huge families demonstrating an X-linked type of heterotaxy. The families where there have been instances of VHS are advised karyotyping but not for all patients on account of high expenses and questionable outcome. None of

Table 1. Showing the pre natal and autopsy findings in our cases.

Fetus sex and age	Echo cardiac findings	Extra cardiac findings	Autopsy findings other than USG findings
20 weeks, male	Levocardia, AVSD, truncus arteriosus, bilateral right atrial appendages. persistent Lt SVC.	Bridging liver, stomach on right side. Aorta and IVC are on left side.	Trilobed bilateral lungs, eparterial bronchi, along with ultrasound findings spleen on right side, Truncated pancreas. Confirmed it as right atrial isomerism.
24 weeks, male	Dextrocardia, AVSD, DORV, bilateral right atrial appendages, TAPVC.	Bridging liver, stomach is slightly central with aorta and IVC on right side.	Trilobed bilateral lungs, eparterial bronchi, bridging liver, spleen at left
19–20 weeks, female	Dextrocardia, AVSD, ToF, pulmonary stenosis, persistent Lt SVC, bilateral right atrial appendages.	Bridging liver, stomach and spleen on Lt side, aorta and IVC Rt side,	Trilobed bilateral lungs, eparterial bronchi, bridging liver confirmed as right atrial isomerism.
24–25 weeks, male	Levocardia, AVSD PAPVD, DORV. Bilateral right atrial appendages	Bridging liver. Stomach on right side, aorta and IVC on left side.	Bilateral trilobed lung, eparterial bronchi. Conformed as right atrial isomerism.
19–20 weeks, female	Dextrocardia, endocardial cushion defect, dilated single outflow tract (CAT), TAPVC.	Bridging liver, stomach on left side.	Bilobed right lung, trilobed left lung, bilateral long bronchi, pancreas truncated. Conformed as VHS.
19 weeks, male	Mesocardiac, broad atrial appendage on left side and sickle shaped appendage on right side & AVSD	Bridging liver, stomach on right side.	Bilateral bilobed lungs and eparterial bronchi. Conformed as VHS
22 weeks, male	Mesocardia, VSD with common arterial trunk, enlarged azygos vein, persistent left SVC.	Bridging liver, stomach on left side.	Bilateral bilobed lungs, hyparterial bronchi, stomach and spleen on left side, gall bladder not visualized, incomplete pancreas, interrupted IVC. Conformed as left isomerism
20 weeks, female	Levocardia, supra cardiac TAPVC, AVSD and transposition of great arteries. Prominent azygos vein and follow-up developed heart block.	Liver on right side. Stomach on left side. Persistent right umbilical vein noted.	Bilateral bilobed lungs, hyparterial bronchi, stomach and spleen on left side. Interrupted IVC noted. Conformed as left isomerism
19 weeks, female	Mesocardia, AVSD, bilateral sickle shaped atrial appendages. Prominent azygos vein	Bridging liver. Interrupted IVC, absent GB and stomach and spleen on right side.	Bilateral bilobed lungs, hyparterial bronchi, malrotated bowel loops. Conformed as left isomerism.
19–20 weeks, female	Dextrocardia, sickle shaped atrial appendages, prominent azygos vein with interrupted IVC	Bridging liver. Stomach and spleen on left side	Bilateral bilobed lungs. Hyparterial bronchi, jejunal atresia conformed as Lt isomerism.
26 weeks, male	Dextrocardia, sickle shaped atrial appendages, AVSD, prominent azygos vein with interrupted IVC	Stomach and spleen are on left side liver is central position. Diagnosed as left isomerism.	Follow-up not available.
28 weeks, male	Levocardia, sickle shaped atrial appendage, interrupted IVC with prominent azygos vein.	Stomach and spleen are on right side. Liver is central in position.	Follow-up not available.

AVSD: atrioventricular septal defect; DORV: double outlet right ventricle; GB: gall bladder; IVC: inferior vena cava; PAPVD: partial anomalous pulmonary venous connection; SVC: superior vena cava; TAPVC: total anomalous pulmonary venous connection; USG: ultrasound; VHS: visceral heterotaxy syndrome; VSD: ventricular septal defect.

Figure 8. Atrial appendages (AA) in isomerism. (a) Right heterotaxy syndrome. (b) Left heterotaxy syndrome. (c) Visceral heterotaxy syndrome.

Figure 9. (a and b) Right and left isomerism showing juxta-position of inferior vena cava (IVC) and aorta (AO). Aorta and azygos (AZY) side by side.

Figure 10. Illustration of four possible atrial appendages. (a) Normal arrangement, (b) mirror imaged arrangement, (c) right atrial arrangement, and (d) left atrial arrangement.

the patients from our study was tried for karyotyping. As the complex cardiac anomalies related to heterotaxy disorders demonstrate a considerable overlap in the prenatal period, and since the postnatal autopsy incorporates the findings that are not reliably assessed in utero (e.g. lung lobulation, bronchial spreading and

Table 2. Summary of major characteristics of the cases.

Characteristics	Right isomerism	Left isomerism	VHS
Diagnosed & confirmed cases	4	6	2
AVSD	4	3. Only VSD in 1	2
Viscerocardiac heterotaxy	4	5	2
Atrial appendages	Bilateral box like AA in 4	Bilateral sickle shaped AA in 6	Rt sickle shaped & Lt box like in 1
Interrupted IVC	Nil	6	Nil
Juxta-position of aorta & IVC	4	Nil	Nil

(continued)

Table 2. Continued

Characteristics	Right isomerism	Left isomerism	VHS
Persistent Lt SVC	2	1	Nil
TAPVC	2	1	Nil
PAPVC	1	Nil	Nil
Heart block	Nil	1	Nil
CAT	1	1	1
DORV	2	Nil	Nil
TGA	Nil	1	Nil
ToF	1	Nil	Nil
Pulmonary stenosis	1	Nil	Nil
Asplenia	1	Nil	Nil
Truncated pancreas	1	1	1
Jejunal atresia, malrotation & absent GB	Nil	1,1&2	Nil

AVSD: atrioventricular septal defect; DORV: double outlet right ventricle; GB: gall bladder; IVC: inferior vena cava; PAPVC: partial anomalous pulmonary venous connection; SVC: superior vena cava; TAPVC: total anomalous pulmonary venous connection; TGA: transposition of the great arteries; ToF: tetralogy of Fallot; VHS: visceral heterotaxy syndrome; VSD: ventricular septal defect.

spleen status). Pre-natal determination of left and right isomerism has generally relied on the presence of heart block, cardiac defects, interruption of IVC, and juxtaposition of the IVC and aorta.³⁰

Conclusion

In this study, we aimed to find common features of heterotaxy syndrome on prenatal ultrasound as well as on fetal autopsy. Our aim is to determine which of the findings can or cannot be helpful on ultrasound examination to diagnose heterotaxy. The examiner should always rule out isomerism when the following ultrasound signs are found: malposition of cardiac and stomach, a complex cardiac defect, fetal heart block, abnormal venous connections, dilatation of the azygous vein, and atrioventricular septal defect associated with conotruncal anomalies. These syndromes should be accurately diagnosed in the prenatal period in order to allow appropriate counseling of parents.

However, in spite of prenatal diagnosis, the prognosis remains poor.

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Authors' Contributions

All authors contributed equally during the preparation of this manuscript.

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