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BRIEF COMMUNICATION

First Trimester Detection of Heart-Hand Syndrome

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Abstract Heart-hand syndrome is a heterogenous group of congenital disorders characterized by upper limb anomalies and congenital heart defects. We report the antenatal scan findings in a 14 week fetus in which bilateral radial ray defect was detected along with cardiac malformations at routine first trimester aneuploidy scan. The cardiac malformations were pulmonary atresia with ventricular septal defect. This was confirmed by clinical and pathological correlation. There are few case reports of early prenatal detection of this syndrome at 14 weeks.

Keywords Holt–Oram syndrome (HOS) · Heart-hand syndrome · Upper limb anomalies · Congenital heart defects · First trimester · Prenatal diagnosis

Introduction

Congenital cardiac and upper-limb malformations frequently occur in association and are classified as heart-hand syndrome [1, 2]. Heart-hand syndrome type I which is the Holt–Oram syndrome (HOS) is a genetically determined disorder in which aplasia or hypoplasia of the thumbs and/or radii are associated with congenital heart disease [2, 3]. It is inherited in an autosomal dominant pattern, characterized by high penetrance and variable expression [4, 5]. The overall prenatal detection rate is low, at about 39 %. Antenatal ultrasound diagnosis of a fetus with heart-hand syndrome having pulmonary atresia with ventricular septal defect (VSD) and bilateral radial ray defects detected at 14 weeks is reported.

Report of Case

A 26-year-old nonconsangiunous couple presented for routine first trimester screening. The woman was a third gravida with history of two abortions. Ultrasound revealed a single live fetus of 14 weeks gestation with a crown rump length of 85 mm. Review of ultrasound reports done elsewhere revealed a nuchal translucency (NT) of 2.8 mm at 11 weeks. In view of an increased NT reported at 11 weeks, a detailed targeted cardiac examination and anatomic survey of the fetus was pursued.

Fetal echocardiography detected normal inflow tracts and a single large outflow tract. Cardiac situs, rate, and rhythm were normal. The four chamber view appeared normal (Fig. 1a) except for a dilated coronary sinus with no asymmetry in cardiac chambers. Five chamber view showed a large overriding aorta with outlet VSD (Fig. 1b). However, a single large vessel was seen in three vessel trachea (3VT) view (Fig. 1c). Three vessel trachea view showed absence of the normal "V" sign which is shown in Fig. 1d. Flow reversal in ductal arch was noted in longitudinal (Fig. 1e) and transverse arch views (Fig. 1f) suggestive of pulmonary atresia with VSD. The pulmonary artery appeared narrow and hypoplastic. Retrograde flow seen in the narrow pulmonary artery was suggestive of pulmonary atresia. Figure 2 illustrates rendered images of the heart with Fig. 2a depicting a four chamber view

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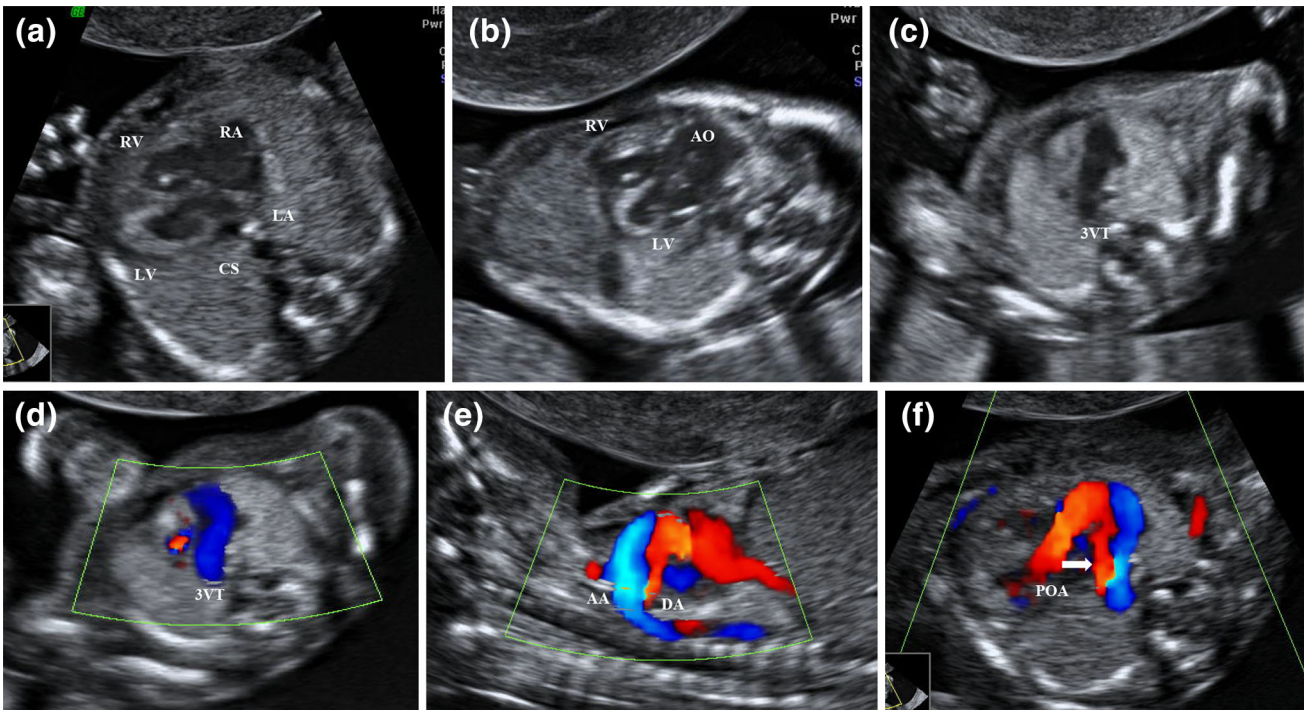

Fig. 1 Transvaginal ultrasound images of fetal heart at 14 weeks. **a** four chamber view, **b** five chamber view showing large overriding aorta, **c** single vessel in 3VT view, **d** 3VT color, **e** longitudinal arch view, **f** flow reversal in ductal arch suggestive of pulmonary atresia

showing dilated coronary sinus, Fig. 2b, c highlighting the overriding aorta. Figure 2d shows persistent left superior vena cava (LSVC) and a single large vessel which is the aortic arch. Radial deviation of hand and shortening of the forearm was evident at 14 week scan as depicted in Fig. 3a.

Bilateral upper limb malformation was more evident in the 16 week scan (Fig. 3c, d). Both upper limbs showed aplasia of radius with hypoplastic thumb. Initially, tetralogy of Fallot was thought of, with a large overriding aorta and narrow pulmonary artery (Fig. 3b) but absence of forward flow in the pulmonary artery led to the diagnosis of pulmonary atresia with VSD. The patient was counseled and re-evaluated at a tertiary fetal medicine unit which confirmed the same findings at 16 weeks. After counseling, the couple opted for termination of pregnancy, and karyotyping along with FISH for DiGeorge syndrome was suggested. The fetal karyotype was normal and no 22q11.2 microdeletion was detected by fluorescence in situ hybridization (FISH). Postnatal pictures are illustrated in Fig. 4a, b.

Discussion

Holt–Oram syndrome is a rare genetic syndrome, characterized by upper limb anomalies and congenital heart defects. Recent molecular genetic studies have determined that mutations in the TBX5 (T-box 5) gene on chromosome 12q24.1 are responsible for both the cardiac and skeletal phenotypic manifestations in this genetic disorder [6, 7]. Mutations in the TBX5 gene are found in approximately 75 % of affected individuals. The condition shows an autosomal dominant inheritance pattern; however, 30–40 % cases result due to de novo mutation. Prenatal sonographic diagnosis of HOS has been scarcely reported in the literature [8] and this usually has been accomplished in HOS-affected parents seeking prenatal diagnosis [9]. The overall prenatal detection rate is low (about 39 %).

HOS represents the most common form of hereditary heart-hand syndromes [10]. Skeletal malformations in HOS are characteristically restricted to the upper limbs in the pre-axial radial ray distribution [3, 10]. Abnormalities of the thumbs may range from absence to a triphalangeal, nonopposable finger-like thumb, whereas, in more severe cases, congenital absence or hypoplasia of the radius and absent thumbs are well-recognized features of the syndrome [3, 4, 10]. Cardiac defects are also characteristic with atrial septal defects of the ostium secundum type being the most frequently found [5, 11].

In a review of the literature involving 189 cases of HOS, single cardiovascular malformations such as atrial septal defect and VSD were found in 125 patients (66 %). However, more complex cardiac defects such as a hypoplastic left heart, total anomalous pulmonary venous

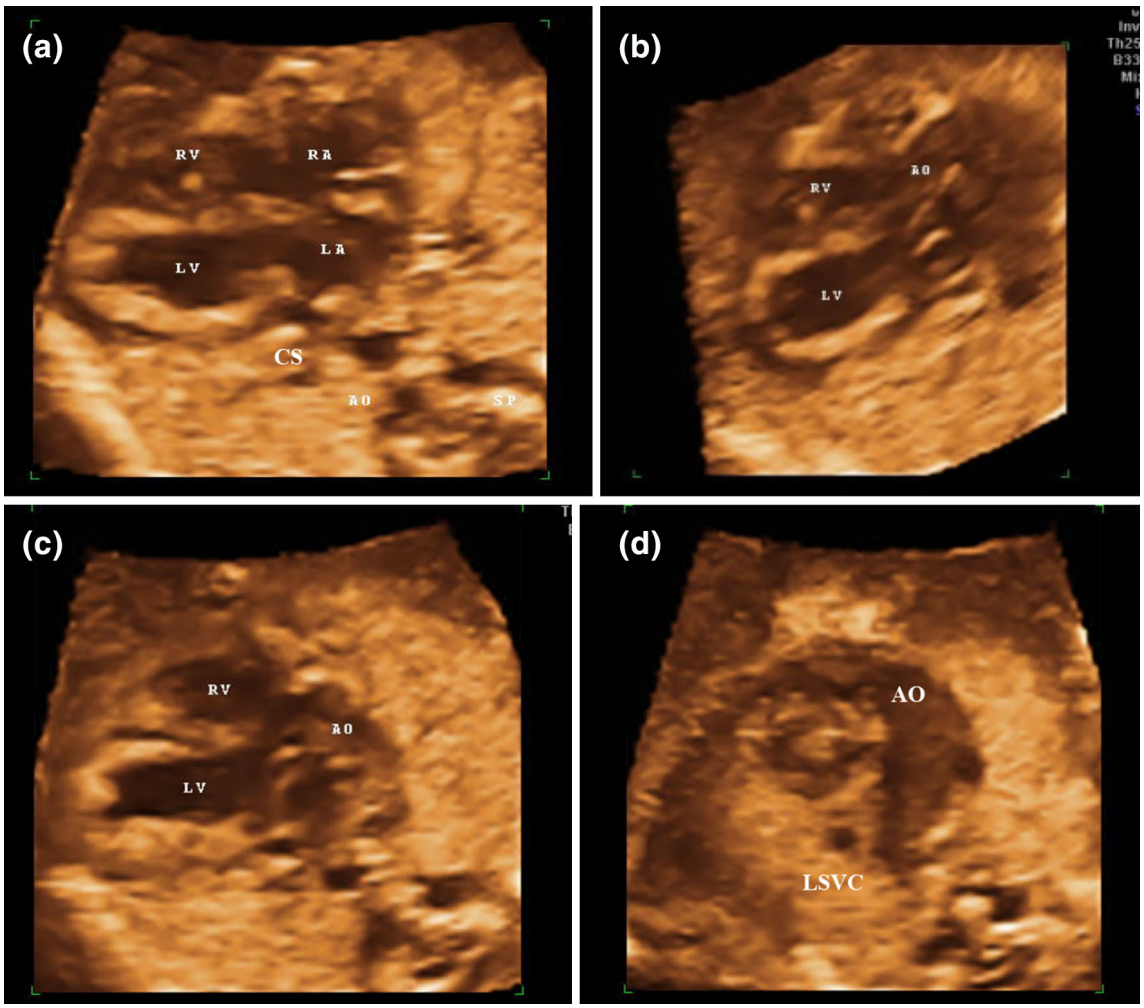

Fig. 2 Four dimensional rendered images of fetal heart, **a** four chamber view showing dilated coronary sinus, **b**, **c** left ventricle outflow tract showing biventricular origin of aorta, **d** three vessel trachea view showing single large vessel and persistent LSVC

return, and truncus arteriosus were reported in an additional 33 patients (17 %), suggesting that severe cardiovascular malformations other than septal defects in patients with HOS could have been underestimated [11, 12].

In the present case, NT thickness of 2.8 mm at 11 weeks was the earliest marker of the cardiac malformation. Increased NT thickness in the first trimester is an important marker of several chromosomal abnormalities, genetic disorders, and cardiac defects [13–15]. The case also highlights the need for looking beyond the four chamber view when evaluating the fetal heart in the 11 – 14 week scan. The initial clue to the cardiac abnormality was the absence of the normal "V" in 3VT view. Normally, in 3VT view color, a 'tick sign' is seen with the short limb formed by the aortic arch and the long limb formed by the ductal arch. This was replaced by the capital "I" sign formed by a single large vessel in the 3VT view (Figs. 1c, d). Detailed sonographic examination of the heart at 14 weeks revealed the cardinal findings of pulmonary atresia with VSD. As bilateral radial ray defect of upper limbs were also detected, the association of all these prenatal findings in the presence of a normal karyotype might be considered specific for heart-hand syndrome. The detection of pulmonary atresia with VSD itself at 14 weeks is a rare entity and to the best of our knowledge, there is no previous report in the literature of this association at 14 weeks. The parents had no phenotypic abnormalities and the possibility of de novo mutation in the fetus was considered though genetic evaluation specific to the syndrome had not been done.

Other disorders in this group of conditions include Tabatznik syndrome (heart-hand syndrome type II), heart-hand syndrome type III, and familial cardiac conduction disease with skeletal malformations [14]. The main differential diagnosis was thrombocytopenia absent radius (TAR) syndrome, an autosomal recessive condition characterized by bilateral radial agenesis and thrombocytopenia, in which cardiac involvement is present in up to 33 %

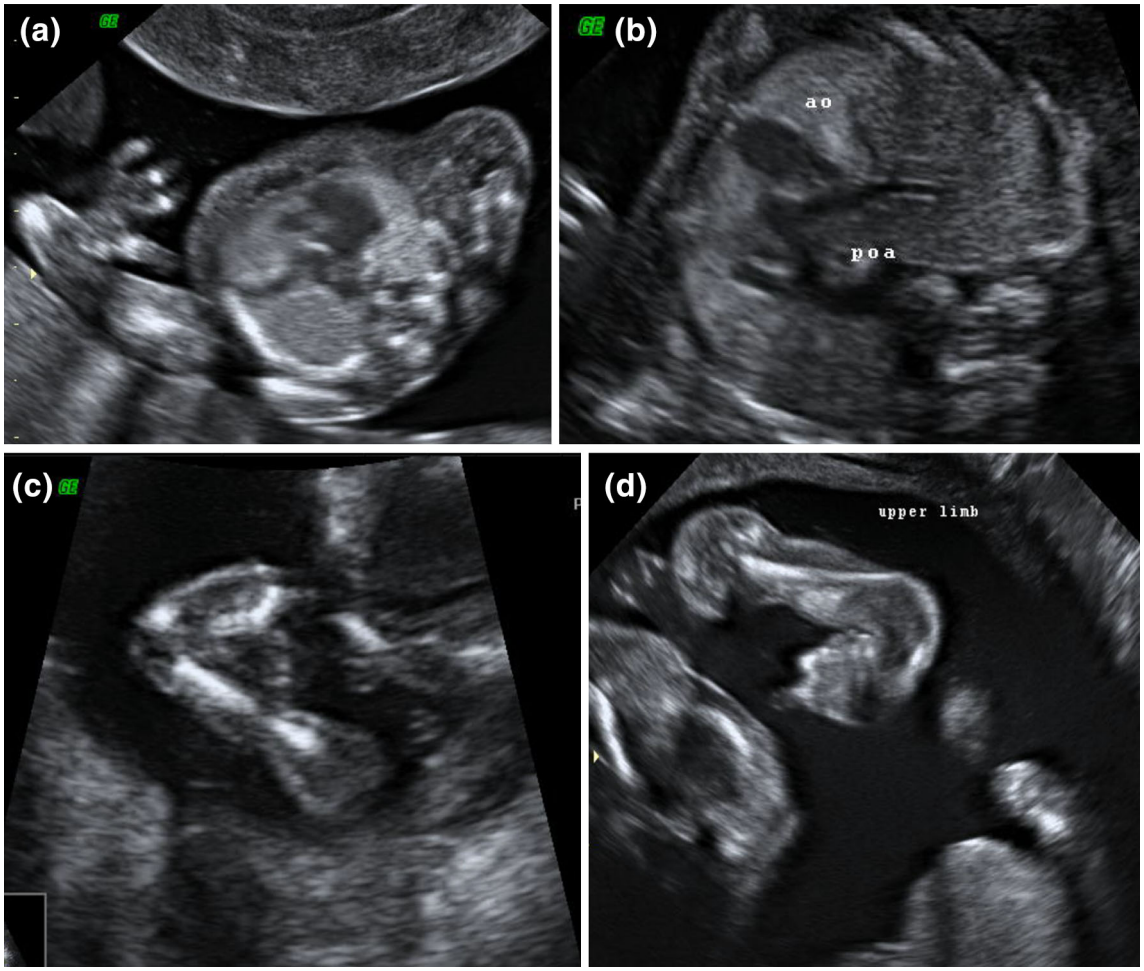

Fig. 3 **a** Ultrasound at 14 weeks showing radial deviation of hand, **b** ultrasound at 16 weeks showing narrow pulmonary artery in three vessel view, **c**, **d** *right* and *left* upper limb at 16 weeks

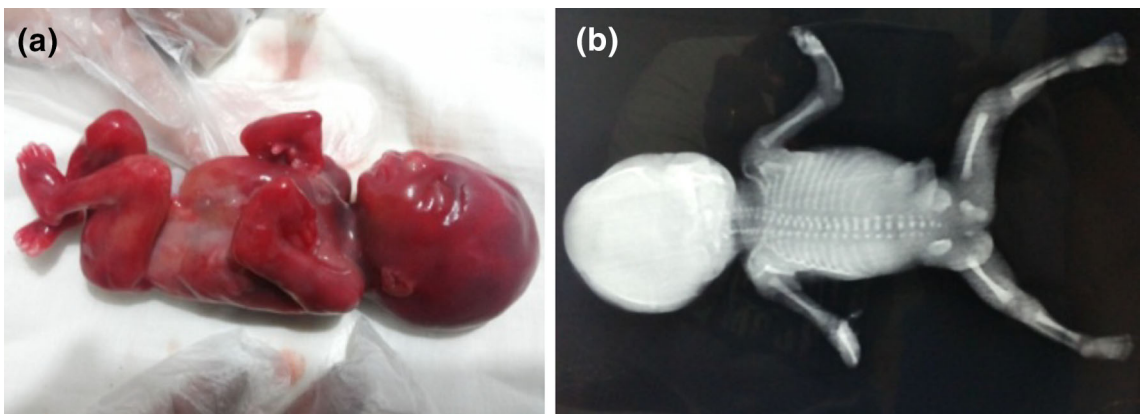

Fig. 4 Postnatal pictures of radial ray aplasia, **a** bilateral upper limb malformation, **b** postnatal fetogram

of cases [16, 17]. Other conditions with cardiac and upper limb abnormalities include Fanconi anemia, McKusick–Kaufman syndrome, VACTERL association, Roberts-SC phocomelia, Okihiro syndrome, fetal valproate syndrome, Nager syndrome, and Edwards syndrome (trisomy 18) [11]. However, the multiplicity of other anomalies in the latter conditions usually makes the prenatal differential diagnosis easy to establish.

Conclusion

The 11–14 week aneuploidy scan, initially meant for measuring the NT, gives us an opportunity for detecting major structural malformations in the fetus. Increased NT is also a marker for cardiac anomaly. Absence of radius and radial deviation of hand is potentially detectable in this period and knowledge of these syndromes would initiate a search to look for other components associated. A detailed evaluation of the fetal heart is necessary at the time of first trimester screening when there is an increased NT, and in the presence of upper limb malformations.

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