CASE REPORT

Prenatal sonographic diagnosis of familial Holt-Oram syndrome associated with type B interrupted aortic arch

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We present a rare case of familial Holt-Oram syndrome diagnosed sonographically at 18 weeks of gestation. The foetus had serious bilateral upper limb malformations, a ventricular septal defect and a type B interrupted aortic arch, while the mother had bilateral upper limb malformations only. The pregnancy was terminated. A pathological and radiological examination of the foetus confirmed the prenatal sonographic findings. Although genetic investigation of *TBX5* mutations was not available in our locality at the time of diagnosis, the geneticists made a clinical diagnosis of familial Holt-Oram syndrome. The clinical features of our case completely fulfilled the strict diagnostic criteria for the syndrome. The cardiac malformations most commonly associated with Holt-Oram syndrome are atrial or ventricular septal defects. To the best of our knowledge, a prenatal diagnosis of Holt-Oram syndrome in association with a type B interrupted aortic arch has not been reported in the English literature before.

Introduction

Holt-Oram syndrome (HOS) is an autosomal dominant disorder, characterised by upper limb malformations and congenital heart disease (CHD).[1] While all individuals with HOS have upper limb malformations, 85 to 95% also have CHD.[2,3] We describe a prenatally diagnosed case of HOS associated with a type B interrupted aortic arch (IAA) and a ventricular septal defect (VSD). To the best of our knowledge, the prenatal diagnosis of HOS with a type B IAA has not been reported in the English literature before.

Case report

In December 2006, a 32-year-old primigravid woman was referred to our prenatal diagnosis clinic at 18 weeks of gestation with a positive second trimester biochemical screening test for Down syndrome. She reported an unremarkable past health and family history. Foetal ultrasonography demonstrated bilateral upper limb malformations (Fig 1). The left upper limb showed aplasia of the radius and ulna and a radial club hand with an absent thumb and the presence of only three digits. The right upper limb showed aplasia of the radius, hypoplasia of the ulna and a radial club hand with an absent thumb. Foetal echocardiography detected a disproportionately dilated right atrium, a large VSD, subaortic stenosis, a small ascending aorta, two arterial branches (the innominate artery [IA] and the left common carotid artery [LCCA]) arising from the ascending aorta, interruption of the

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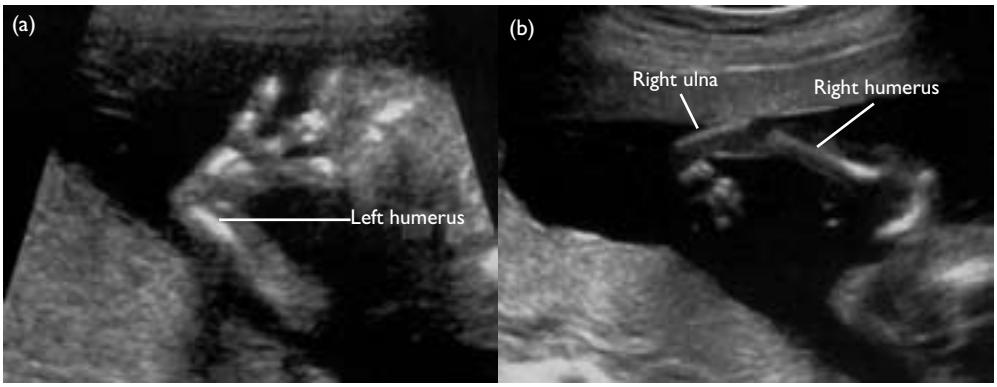

FIG 1. Ultrasound pictures demonstrate bilateral upper limb malformations
(a) Left upper limb showing radial and ulnar aplasia and radial club hand with an absent thumb and presence of only three digits. (b) Right upper limb showing aplasia of radius, hypoplasia of ulna and a radial club hand with an absent thumb

家族性霍—奧綜合症伴有乙型大動脈弓中斷之產前診斷

本文報告一宗在懷孕18周利用超聲波檢查診斷出的罕有家族性霍—奧綜合症個案。個案中的胎兒患有嚴重兩側上肢畸型及乙型大動脈弓中斷和心室間隔缺損，而孕婦卻只有兩側上肢畸型。孕婦決定終止懷孕。胎兒的病理及X光檢查確認了產前超聲波檢查的發現。雖然在診斷此個案時，本地還沒有*TBX5*遺傳因子突變化驗，但因為本個案的臨床病徵完全符合霍—奧綜合症的嚴格診斷標準，所以遺傳科醫生仍然能夠作出霍—奧綜合症的臨床診斷。大部份出現在霍—奧綜合症的先天性心臟病是心房間隔或心室間隔缺損。據我們所知，在產前診斷出的霍—奧綜合症而同時又出現乙型大動脈弓中斷的個案，在此報告之前是從來沒有在英文文獻上出現過的。

aortic arch distal to the LCCA (type B IAA), another artery (the left subclavian artery [LSA]) arising from the descending aorta, a dilated pulmonary artery and a persistent left superior vena cava (Fig 2). The heart rate and rhythm were normal. After having the findings explained, the woman disclosed a history of bilateral upper limb deformities since birth. Her orthopaedic records were then traced, and these revealed bilateral hypoplasia and chronic dislocation of the radial heads, a fused scaphoid-lunate and trapezium-trapezoid-capitate of the left wrist, a fused trapezium-trapezoid-capitate of the right wrist, bilateral hypoplastic thumbs and bilateral absence of the thenar eminence. Functionally, she had absence of forearm rotation on both sides, absence of bilateral thumb interphalangeal joint flexion and bilateral stiff thumb carpo-metacarpal joint movements. Despite these functional abnormalities, her activities of daily living were not seriously affected.

Amniocentesis was performed to exclude chromosomal abnormalities and microdeletion of chromosome 22q11.2. The foetal karyotype was normal (46,XY) and no 22q11.2 microdeletion was detected by fluorescence in-situ hybridisation (FISH). At the mother's request, the pregnancy was terminated medically. Pathological and radiological examinations of the foetus confirmed the prenatal sonographic findings. No anomalies beyond the upper limb and the cardiac malformations were found. The patient was assessed, using echocardiography, by a private cardiologist and no significant CHD was found. Since the overall picture suggested a diagnosis of familial HOS, she was referred to the Clinical Genetic Service for genetic diagnosis and counselling. After reviewing the foetal postmortem findings and the mother's clinical features, the geneticists made a diagnosis of familial HOS. Genetic studies for *TBX5* gene mutations were not performed as this investigation was not available in our locality at that time. The autosomal dominant inheritance pattern in HOS and the 50% risk of its occurrence in future offspring were explained to the woman.

Discussion

Holt-Oram syndrome is an inherited disorder with an autosomal dominant transmission, which is highly penetrant and markedly variable in clinical expression. The genetic defect involves mutations in the *TBX5* transcription factor gene located on chromosome 12q24.1.[4,5] Both the upper limb and the cardiac malformations vary widely in their severity, which may not correlate with each other. The severity of malformations may also vary among affected members of the same family. Offspring may inherit both skeletal and cardiac defects from parents with skeletal malformations only. In our case, the mother had no CHD and relatively mild upper limb malformations, but her foetus had serious skeletal and cardiac malformations. Holt-Oram syndrome is rarely reported prenatally. This is because, firstly, it is a rare syndrome with a prevalence of 1 in 100 000 total live births[6] and secondly, 85% of cases of HOS are caused by new mutations,[6] so most do not have risk factors that warrant detailed prenatal ultrasonography. Thirdly, some cases may have very subtle skeletal malformations and absent or mild CHD that escape prenatal sonographic detection.

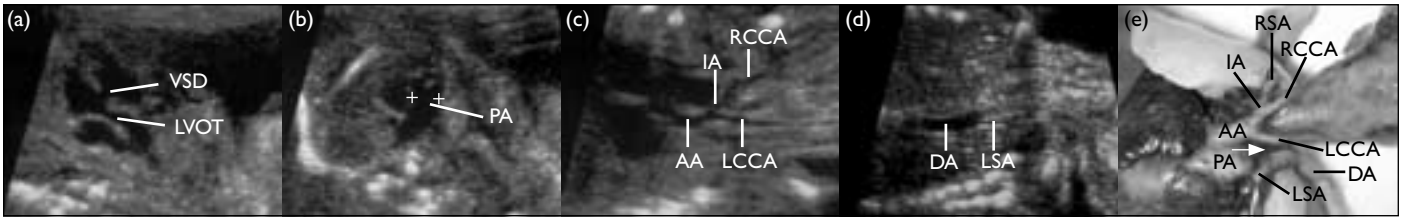

FIG 2. Ultrasound and pathological pictures demonstrate cardiac malformations

(a) Long-axis view showing ventricular septal defect (VSD) and narrowing of left ventricular outflow tract (LVOT). (b) Transverse view of the pulmonary trunk showing dilated pulmonary artery (PA). (c) Long-axis view of the aortic arch demonstrating (i) the site of interruption distal to the left common carotid artery (LCCA) and (ii) the ascending aorta (AA) running straight upward to branch into the innominate artery (IA) and the LCCA instead of forming an arch. (d) Longitudinal view showing the left subclavian artery (LSA) arising from the descending aorta (DA). (e) Pathological specimen confirming the ultrasound findings—note the site of interruption (arrow) between the ascending aorta (AA) and the descending aorta (DA), which was unfolded for better visualisation

Holt-Oram syndrome is the most common form of the heart-hand syndromes, which are a group of genetically heterogeneous disorders characterised by combined upper limb malformations and CHD.[2] Other forms of heart-hand syndromes include Tabatznik syndrome (Heart-Hand syndrome type II) and Heart-Hand syndrome type III.[2] Apart from the rare heart-hand syndromes, other congenital disorders may also be phenotypically similar to HOS, like Fanconi's anaemia, thrombocytopaenia absent radius syndrome, VACTERL association, Roberts-SC phocomelia, Okihiro syndrome, trisomy 18, and foetal valproate syndrome. A combination of upper limb malformations and CHD may also occur with a variety of structural anomalies.[3,7] These probably represent different conditions as no mutations in *TBX5* have been found in patients with atypical features.[3,7] It is important that HOS is differentiated from conditions with overlapping phenotypes because the aetiology, range of congenital defects, prognosis and mode of transmission may be very different. Although genetic studies for *TBX5* mutations can differentiate HOS from similar conditions, the use of strict clinical criteria to make an accurate diagnosis of HOS is still important because *TBX5* genetic studies may not be available in every locality. It is also unlikely that one can detect mutations in all affected cases in single gene diseases. Linkage studies for cases with absent *TBX5* mutations are not possible if the family size is small or the affected cases are sporadic. Moreover, McDermott et al[7] demonstrated that the addition of adherence to strict HOS diagnostic criteria to *TBX5* mutational analysis provided a markedly increased sensitivity in genetic testing for HOS—rising from 26 to 74%. Clinical criteria diagnostic of HOS include pre-axial radial ray malformations in at least one upper limb and cardiac septation (atrial septal defects [ASD] or VSD) or conduction defects.[6-8] Congenital heart diseases may not be present, and, when this is the case, there should be a family history of HOS with inheritance consistent with an autosomal dominant pattern.[3] Lower limb and isolated post-axial upper limb malformations are not skeletal features of HOS.[7] Congenital abnormalities affecting other organs and intellectual deficits are also atypical of HOS.[3,7] In our case, the clinical features of the woman and her foetus completely fulfilled the strict diagnostic criteria for HOS.

According to the literature review by Sletten and Pierpont,[9] ASD were the most common form of CHD found in HOS, occurring in 60.3% of cases, either singly or in combination with other cardiac defects. While 66.1% of all cardiac abnormalities were mild single abnormalities, mostly ASD or VSD, 17.5% had moderate to serious combination defects. In our case, the foetus had a type B IAA with a VSD. Interrupted aortic arch is a rare congenital anomaly and has been classified into three types by Celoria and Patton[10] according to the site of aortic interruption. The arch is interrupted distal to the LSA in type A, between the LCCA and the LSA in type B and between the IA and the LCCA in type C. Type B, the most common form of IAA, is considered to be aetiologically different from type A. Type A IAA is believed to be closely related to coarctation of the aorta pathogenetically,[11] and thought to be due to abnormal blood flow during embryogenesis. It may be an extreme form of aortic coarctation. On the other hand, type B IAA is believed to be a conotruncal defect caused by a developmental anomaly of the bronchial arch system. According to a study in a large, prospectively ascertained sample of patients with conotruncal defects, microdeletion of chromosome 22q11.2 was found in patients with type B IAA (57.1%), but not in those with type A.[12] In our case, microdeletion of chromosome 22q11.2 was excluded in the foetus using FISH. The association of type B IAA with HOS in our case suggests that conotruncal defects may develop in HOS. In fact, conotruncal defects like the tetralogy of Fallot and truncus arteriosus have been shown to occur with HOS.[3,7-9] In type B IAA, a VSD is found in about 80% of the cases.[13] Posterior displacement of the infundibular septum causes a malalignment VSD and subvalvular aortic stenosis. There is usually absence of a pressure gradient between the left ventricle and the ascending aorta. This is probably due to left to right shunting of blood through the VSD, which in turn causes dilatation of the pulmonary artery and narrowing of the ascending aorta.[14] These features were all observed in our case. The aortic valve is frequently bicuspid, with or without obstruction. There may also be an associated aberrant right subclavian artery,[14] that was not present in our case.

In conclusion, we report a rare case of prenatal diagnosis of familial HOS associated with type B IAA at 18 weeks of gestation. Although the diagnosis was not documented by proven *TBX5* mutations because of unavailability of the test in our locality at the time of diagnosis, we believe that this is a true case of HOS as the clinical features fit the strict diagnostic criteria for HOS perfectly.

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