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, the 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). While all individuals with HOS have upper limb malformations, 85 to 95% also have CHD. 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
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. 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 and secondly, 85% of cases of HOS are caused by new mutations, 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](image-url)
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. Other forms of heart-hand syndromes include Tabatznik syndrome (Heart-Hand syndrome type II) and Heart-Hand syndrome type III. Apart from the rare heart-hand syndromes, other congenital disorders may also be phenotypically similar to HOS, like Fanconi's anaemia, thrombocytopenia 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. These probably represent different conditions as no mutations in TBX5 have been found in patients with atypical features. 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 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. 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. Lower limb and isolated post-axial upper limb malformations are not skeletal features of HOS. Congenital abnormalities affecting other organs and intellectual deficits are also atypical of HOS. 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, 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 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, 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. 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. In type B IAA, a VSD is found in about 80% of the cases. 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. 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, 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.

References

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