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Holt Oram syndrome: a case report and review of the literature

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Summary

Holt Oram syndrome is a rare autosomal dominant syndrome on average, of varying severity, which may result in heterogeneous pictures, predominantly with involvement of the bony segments of the upper limbs and the cardiovascular system. The syndrome is caused by mutations in two genes of the T-box (TBX5, 601 620 and TBX 3) located on the 12q24.1p. The authors report a case and review the literature.

Key words: Holt Oram syndrome; Obstetric ultrasound.

Introduction

Holt Oram syndrome is a rare autosomal dominant syndrome on average, of varying severity, which may result in heterogeneous pictures, predominantly with involvement of the bony segments of the upper limbs and the cardiovascular system. Mary Holt and Samuel Oram described it for the first time in 1960, and since then several authors [1-13] have reported more than 300 cases. The presence of cardiac abnormalities, muscle, and bone inspired a number of names for this syndrome, such as "heart-hand syndrome", "syndrome heart-upper", and "upper limb cardiovascular syndrome". The syndrome is caused by mutations in two genes of the T-box (TBX5, 601 620 and TBX 3) located on the 12q24.1p. The TBX5 gene is only involved in the development of the upper limb. The prevalence is estimated to be 0.95 cases per 100,000 births, shows a penetrance of 100%, with a recurrence risk of 50%. About 85% are due to new mutations [1-12, 14-19].

Case Report

The authors report here a case of a patient with a syndromic fetus admitted to the Gynecologic and Obstetric Clinic of the University of Sassari in 2013. The case concerned a Caucasian 36- year-old patient at 19 weeks and three days gestation with parity 2012 (two vaginal deliveries in 2001 and 2005 respectively, and one miscarriage at 22 weeks). The patient did not smoke and reported to have the common childhood rashes. A family history indicated the presence of a sibling suffering from Trisomy 21.

Nuchal Translucency (NT) showed a combined risk in the standard range (1: 8071) and a value of NT of 1.1 mm. The patient underwent chorionic villus sampling which demonstrated a set of 46, XX (normal female karyotype). The diagnostic ultrasound allowed the authors to study the fetal morphology in detail. The gestational age was recalculated at 18 weeks and three days.

The authors reported multiple malformations in the upper extremities. An agenesis was estimated of the radius at level of both forearms, with agenesis of the first fingers in the hands. The humerus and ulna, and shoulder blade were found to be normally represented in morphology and size. There was no malformation nor anomaly at the level of the bony component of the carpus [7-9, 14]

At the cardiac level no morphological abnormality were observed. The scanning of the apical four chambers and in combination with color Doppler showed a normal left situs, no rhythm abnormalities, and normal aortic arch. Particular attention was paid to assess the presence of direct and indirect signs of atrial and ventricular septal defects that were not detected [4]. The patient expressed her desire to terminate the pregnancy. The woman underwent a cycle of vaginal prostaglandin at the end of which vaginal abortion was carried out.

The fetus (Figure 1) showed gross malformations such as lack of thumbs and bilateral syndactyly of II and III fingers of the right hand. The placenta was subjected to histological examination: weight of 170 grams and dimensions of 11×10×4 cm with a cord of 22 cm without any special pathological notes; focal hemorrhagic areas in the context of the placenta were detected.

The fetus was subjected to X-ray (Figure 2) that showed a bilateral agenesis of the radius and the second toe on both ends. External examination showed the fetus pronate both hands and deflected medially associated with bilateral agenesis of the thumbs and fifth fingers spaced with respect to the other fingers. In the right hand there was also present syndactyly between II and III finger. External genitalia were female type. Internal examination in the forearm confirmed bilateral agenesis of the radius. Organs of the chest, head, abdomen, and pelvis showed no obvious macroscopic pathologies.

Discussion

Cardiac lesions, which may be present in complex forms in 17% of cases, include an atrial septal defect (30-60%) and ventricular patency of the ductus arteriosus, hypoplastic left ventricle, conduction abnormalities, and disruption of the aortic arch. Among the septal defects, the most frequently represented in 34% of cases are those

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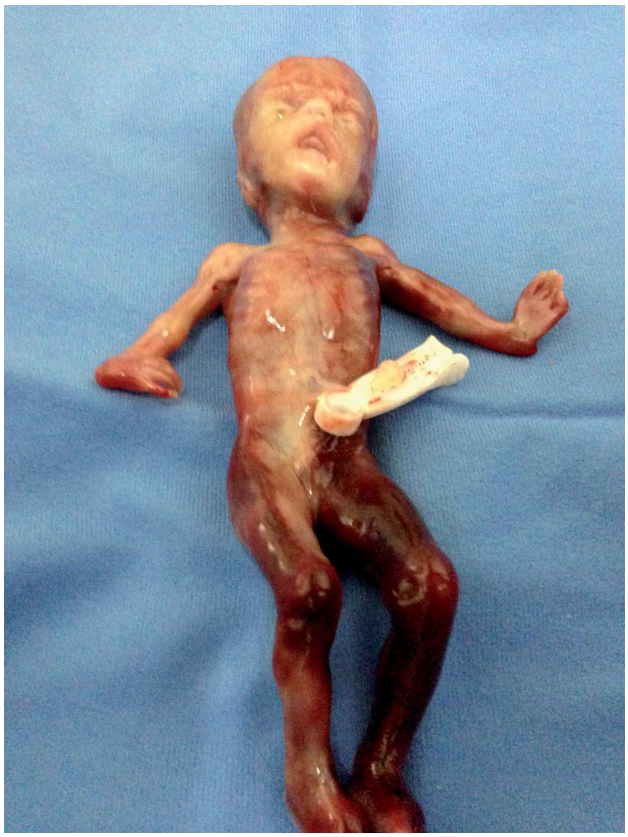

Figure 1. — Macroscopic evaluation of the fetus showing the upper limb malformations.

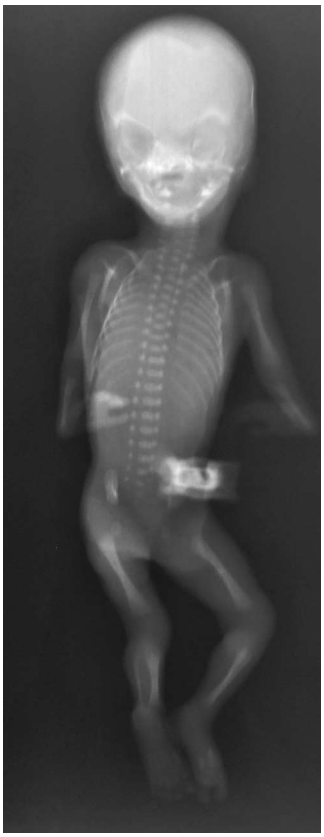

Figure 2. — X-ray confirming upper limb malformations.

of the secundum. Skeletal abnormalities save the lower limbs: this is because in the mutant gene interferes with the differentiation during the fourth and fifth weeks of pregnancy, when the lower limbs have not yet entered in the phase of differentiation. The anomalies of the upper limbs occur mainly at the expense of high radial and manifest as radial aplasia, triphalangeal thumb or absent, hand pie, shortness clavicular, radio-ulnar synostosis and marked prominence of the medial epicondyle, pectus excavatum, structural abnormalities of the scapula, the humerus and the ulna, to cases of phocomelia. Often the left side is more involved.

Patients that have a normal mental development and motor development may be compromised only in relation to the degree of involvement of the upper limb and scapular girdle. The patients have a life expectancy that depends primarily on the severity of the cardiac lesion. Though usually Holt Oram syndrome is not fatal, surgeries and aggressive therapies may be necessary.

The variable expressivity of the disease requires a careful examination of the family to determine whether the mutation is segregating (recurrence risk 50%) or recent (negligible risk). Identification of patients with minimal expression of the gene is difficult and clinical examination should include a search of electrocardiographic abnormalities, the bones of the carpus, and the study of the metacarpophalangeal profile.

Prenatal diagnosis is crucial for appropriate counseling, with the option of a termination of pregnancy. Although there are several cases [1-15] in the literature, there are few descriptions of prenatal diagnosis, precisely because of the high variability with which the syndrome occurs. Ultrasound diagnosis therefore focuses on the research of cardiac morphology (projection of the four chambers and axial) and the aortic arch, and all segments of the upper limb musculoskeletal. The diagnosis can be facilitated by a comparison of the increase in the value of NT. Differential diagnosis should be considered according to ultrasound conditions involving the radial ray defects, especially "thrombocytopenia with absent radius syndrome" also known as TAR (autosomal recessive syndrome presenting unilateral or bilateral agenesis of the radius, the normal development of the thumb and fetal thrombocytopenia), the VATER association, Trisomy 13, Trisomy 18. Platelet count by cordocentesis, karyotype analysis, the absence of radiological abnormalities ultrasound before and during the neonatal period, and the absence of cardiac anomalies, exclude the aforementioned diseases.

The present case is an example of how this syndrome may appear in completely heterogeneous, being characterized by only part of the anomalies that normally constitute it.

The suspected diagnosis of this syndrome should be strongly influenced by the presence of anamnestic cases in the family of one or both parents. Diagnostic ultrasound allows to enter the fetus suffering from this syndrome to a procession of syndromes with similar abnormalities. The exclusion of individual anomalies, cordocentesis, and karyotype analysis are further means of diagnostic orientation. Currently, the research of the genetic anomaly on abortion material and blood sampling of both parents was received. The data collected until now allowed diagnosis. The definitive diagnosis was only possible as a result of the molecular response to the presence of the mutation on genes TBX5 and TBX3.

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