CASE REPORT

Holt–Oram Syndrome: The Importance of Prenatal Detection

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Abstract

Aim: The aim of the paper is to present prenatal diagnosis of Holt–Oram syndrome (HOS), pregnancy management, out-of-hospital birth in the 33rd week of gestation, and postnatal treatment.

Case description: The following fetal malformations were detected by ultrasound on the 30th week of gestation: bilateral upper lip and palate cleft, bilateral upper limb mesomelia with bilateral ulnar deviation of the wrist with absent thumb, ventricular septal defect, and distension of the colon. The amniotic fluid index was 23. Holt–Oram syndrome was suspected. During the ultrasound examination, a Kurjak antenatal neurodevelopmental test (KANET) was scored to be 8. At home, at the 33rd week of pregnancy, a premature rupture of the amniotic membranes occurred, followed by uterine contractions, and the patient was urgently transported to the hospital. During the transportation attended by the midwife, premature baby was delivered in the car not far from the hospital, where the baby was admitted at the age of 7 minutes. The baby was admitted to the neonatal intensive care unit with all prenatally detected congenital malformations present during the first check-up. The baby was in the life-threatening condition and died at the age of 48 hours.

Conclusion: Holt–Oram syndrome should be prenatally detected in order to enable better prenatal counseling with the possibility of the interruption of pregnancy, which may be the option in severe cases, or if parents opt for continuation of pregnancy to discuss with the all possible options of pregnancy and postnatal outcome.

Keywords: Congenital heart defect, Holt–Oram syndrome, Prenatal diagnosis, Screening.

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Introduction

Holt–Oram syndrome (HOS) is a rare autosomal dominant disorder.[1] It is characterized by skeletal abnormalities of the upper limbs and congenital heart defects (CHDs) (structural CHDs and/or cardiac rhythm disorders).[1–3] Structurally, an ostium secundum atrial septal defect (ASD) or a ventricular septal defect (VSD) are the most common CHDs.[2,3] Clinical diagnosis is established by the presence of preaxial radial ray malformations in at least one upper limb and the presence of CHDs and/or cardiac conduction defects.[4] The prevalence is 0.7–1 on 100.000 newborns.[5] The prenatal detection rate is small, around 39%.[6]

The aim of the paper is to present prenatal diagnosis of HOS, pregnancy management, out-of-hospital birth in the 33rd week of gestation, and postnatal treatment.

Case Description

The patient was 19-years-old, primipara without previous abortions. In her medical history, there was no data about genetic diseases or malformations in her family or the husband's family. The patient lived in a rural environment and didn't control her pregnancy regularly. During the pregnancy, neither an ultrasound nor biochemical screening was done. At the 30th week of gestation, an increased amount of amniotic fluid was noted at the outpatient primary care center, which prompted referral to the tertiary care perinatal center at the Clinic for Gynecology and Obstetrics, Clinical Center University of Sarajevo, where the patient was hospitalized for further evaluation. The following malformations were detected during expert ultrasound evaluation: bilateral upper lip and palate cleft, bilateral upper limb mesomelia with bilateral ulnar deviation of the wrist with absent thumb, ventricular septal defect, and distension of the colon. The amniotic fluid index was 23. Holt–Oram syndrome was suspected (Figs 1 to 4). During the ultrasound examination, a Kurjak antenatal neurodevelopmental test (KANET) was scored to be 8 (borderline). The facial expressions of the fetus were almost completely absent. Laboratory tests were uneventful. The patient and her husband were provided with

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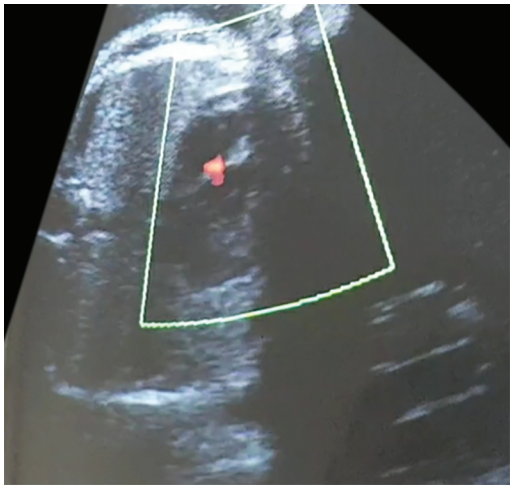

Fig. 1: Ventricular septal defect

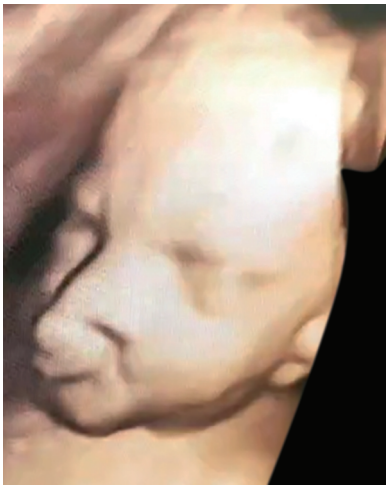

Fig. 2: Bilateral cleft lips

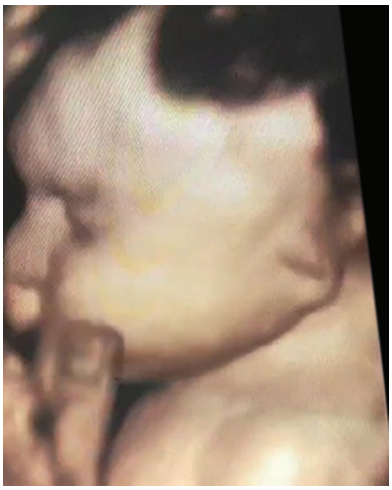

Fig. 3: Low-set ears

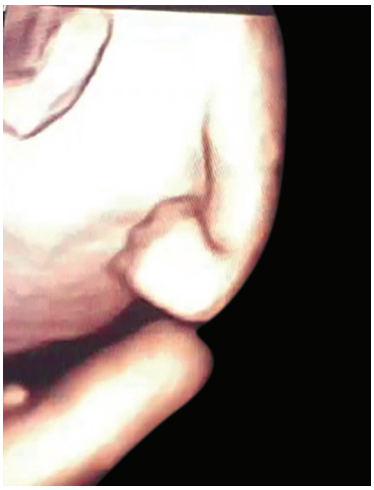

Fig. 4: Mesomelia

complete information about the condition of the fetus. The patient was discharged home and follow-up appointment was scheduled in 15 days.

At home, at the 33rd week of pregnancy, a premature rupture of the amniotic membranes occurred, followed by uterine contractions, and the patient was urgently transported to the hospital. During the transportation attended by the midwife, a premature baby was delivered in the car not far from the hospital, where the baby was admitted at the age of 7 minutes. The baby was admitted to the neonatal intensive care unit with all prenatally detected congenital malformations present during the first check-up (Fig. 5). The baby was in the life-threatening condition, resuscitated, mechanically ventilated, and died at the age of 48 hours.

The patient refused postmortem pathohistological and cytogenetic analysis. The postnatal course of the mother was uneventful.

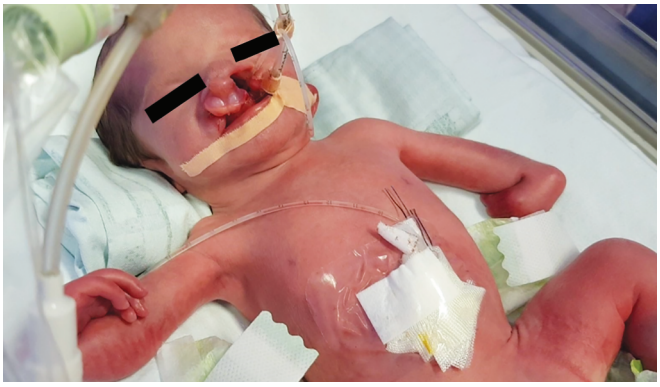

Fig. 5: Newborn on mechanical ventilation

Discussion

The diagnosis of HOS is based on the clinical findings, family history, as well as the presence of genetic changes (mutations or pathogenic variants) of the TBX5 gene (locus 12q24).[1,7] The course of HOS may be from intrauterine death to postnatal death or liveborn baby with unrecognized HOS till adulthood in mild cases. About 75% of patients diagnosed with HOS may have cardiac defects like ventricular septal defect (VSD), atrial septal defect (ASD), patent ductus arteriosus (PDA), aortic atresia, tetralogy of fallot (TOF), double outlet right ventricle, infundibular pulmonary stenosis, complete atrioventricular (AV) canal, mitral valve prolapse, hypoplastic left heart syndrome, coarctation of the aorta, subaortic

stenosis, or left ventricular noncompaction syndrome.[6–10] There are also isolated cases when the diagnosis is made in adulthood.[11] The most common changes in cardiac conduction present as bradycardia, deteriorating with advancing patient's age (atrial fibrillation, atrial flutter, and interventricular arrhythmias have been reported).[11] When associated with ASD, it is HOS type I; Tabatznik syndrome is type II (arrhythmias and brachytelephalang); the Spanish variant is type III (arrhythmia and brachydactyly type C); the Slovenian variant is type IV (arrhythmia, dilatative cardiomyopathy, brachydactyly).[12,13] Changes on the upper limbs can range from an abnormal carpal bone or triphalangeal thumb to bilateral phocomelia; sometimes the only pathology can be a delayed carpal bone age.[12] Radial defects are the most common changes.[14] It was first described by Mary Clayton Holt and Samuel Oram in 1960.[8]

Prenatal diagnosis of HOS is of particular importance. Changes in the radius and ulna can be seen from 13 to 16 weeks of gestation, and most of the CHD (except ASD and small VSD) can be detected from 18 to 20 weeks of gestation. Barisic et al. in an analysis of 34 registers in the period 1990–2011, with a total of 73 cases of HOS, stated that over 60% of cases were not suspected prenatally, although they could be noticed in pregnancy.[1] The same authors state that in a total of 20 cases that were prenatally detected, 9 parents did not choose to terminate the pregnancy.[1] The same case was with our patient. The prognosis of HOS patients is varied and depends on the symptomatology itself and the complexity of the cardiac disorders.[15] A multidisciplinary approach to this type of patient is vital and includes a gynecologist who is specialized in fetal echocardiography, a pediatric (and adult) cardiologist, an orthopedist, a geneticist, and an immunologist.[16,17] Almost 74% of patients with clinical HOS criteria will also have mutations in the TBX5 gene (prenatal detection is possible, and TBX5 genotyping has high sensitivity and specificity for HOS).[18] It is very important to pay attention to family history, and sometimes, even though it is negative, it does not mean that HOS does not exist in the family tree (sometimes the symptoms are unrecognized).

Conclusion

Holt–Oram syndrome should be prenatally detected in order to enable better prenatal counseling with the possibility of the interruption of pregnancy, which may be the option in severe cases, or if parents opt for continuation of pregnancy to discuss with the all possible options of pregnancy and postnatal outcome.

Declaration of Patient Consent

The authors certify that they have obtained the patient consent forms from parents.

Author's Contribution

Edin Medjedovic, Nedim Begic, and Edin Begic gave substantial contribution to the conception or design of the work and in the acquisition, analysis, and interpretation of data for the work. Edin Medjedovic, Edin Begic, Zijo Begic, Amer Iglica, Alma Suljevic, and Edin Medjedovic had role in drafting the work and revising it critically for important intellectual content. Each author gave final approval of the version to be published and they agree to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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