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We report on the association of Mayer–von Rokitansky–Küster–Hauser syndrome (MRKHS) with a unique form of Holt–Oram syndrome (HOS) with an aorto-pulmonary window. A 24-year-old Turkish woman was referred to our hospital because of primary amenorrhoea. Both her vagina and uterus were absent, and the diagnosis of MRKHS was established. Laparoscopic creation of a neovagina by the modified Vecchietti technique was performed. A rare congenital malformation of the heart, namely an aorto-pulmonary window, had required cardiac surgery when the patient was a 6-month-old infant. This cardiac malformation plus associated upper limb anomalies led to the clinical diagnosis of HOS. To the best of our knowledge, this is only the second report in the scientific literature on the concurrence of MRKHS and HOS, and the first published case of HOS with an aorto-pulmonary window as the cardiac malformation.

Key words: heart–hand syndrome/Holt–Oram syndrome/Mayer–von Rokitansky–Küster–Hauser syndrome/neovagina/Vecchietti’s technique

Introduction

Mayer–von Rokitansky–Küster–Hauser syndrome (MRKHS) is characterized by the congenital absence of the vagina and a variety of Müllerian duct anomalies, with aplasia of the uterus being the most common. In general, these patients have normally functioning ovaries which are often located at the pelvic brim. Consequently, these women do not experience a menarche while having well developed secondary sexual characteristics. MRKHS frequently is associated with anomalies of the urinary tract and the skeleton. The skeletal disorders, occurring in ~10–15% of cases (Fakih et al., 1987), mostly concern the vertebra, the ribs or the upper limbs. In addition, an inguinal hernia occurs quite frequently. The incidence of the syndrome ranges from 1:4000 (births) to 1:20 000 (female hospital admissions) (Giatras et al., 1998). MRKHS is sporadic, with the pedigree pattern being consistent with an autosomal dominant trait. The karyotype of the patients is always female (46, XX). Aetiologically, a non-fusion of the Müllerian duct with the Wolffian duct and a deficiency of progesterone and/or estrogen receptors have been discussed (Ludwig, 1998). This deficiency leads to an arrest in the further development of the embryonic Müllerian duct with subsequent faulty differentiation of the structures. Because of normal sexual development, the syndrome usually remains undetected until primary amenorrhoea and/or difficulty in attempting sexual intercourse result in the diagnosis.

Holt–Oram syndrome (HOS), also referred to as heart–hand syndrome, is characterized by congenital heart abnormalities and skeletal malformations of the upper limb, ranging from subtle changes, such as hypoplasia or absence of the thumb (Fakih et al., 1987), to frank phocomelia, with the left side usually being more severely affected (Holt and Oram, 1960; Smith et al., 1979; Bossert et al., 2002). It is a monogenic disorder, inherited in an autosomal dominant trait with complete penetrance and variable expression in the affected families (Basson et al., 1997). The HOS gene is mapped to the long arm of chromosome 12 (12q24.1) and encodes a T-box-containing transcription factor (TBX5). An analysis of the variable expressivity of HOS by mutation screening in 55 subjects with HOS suggests that neither the type of mutation in TBX5 nor the location of a mutation in the T-box is predictive of the expressivity of malformations in individuals with HOS (Brassington et al., 2003). Despite the autosomal dominant inheritance of HOS, females are predominantly and more severely affected (Newbury-Ecob et al., 1996). The most common cardiac defects associated with HOS are ostium secundum atrial septum defect (in ~60% of the cases), followed by ostium primum atrial septum defect and ventricular septum defect (Sletten and Pierpont, 1996). However, a wide variety of complex cardiac anomalies may occur in HOS, such as mitral valve prolapse, tetralogy of Fallot, hypoplastic left heart syndrome and tricuspid atresia (Zhang et al., 1986; Glauser...
et al., 1989; Lehner et al., 1994; Bossert et al., 2002). These anomalies may be accompanied by a variety of supraventricular and ventricular electrocardiogram (ECG) abnormalities, consisting of conduction or pacemaker disturbances up to complex arrhythmia (Zhang et al., 1986). In addition, anatomical anomalies of the large vessels have been reported, including patent ductus arteriosus, hypoplastic pulmonary artery and persistent left superior vena cava (Massumi and Nutter, 1966; Solit et al., 1973). An aorto-pulmonary window (APW) is a rare cardiac malformation and was first described by Elliotson (1830). In 90% of patients, it consists of a large oval defect between the ascending aorta and the pulmonary trunk. The APW normally should be closed either by surgical or by interventional techniques (i.e. umbrella closure) before irreversible changes of the pulmonary vessels develop (Tulloh and Rigby, 1997). Hitherto, and to the best of our knowledge, APW has not been described in association with HOS (MEDLINE/PubMed search).

Case report

A 24-year-old Turkish woman with previously diagnosed HOS was referred to our out-patient department with primary amenorrhoea. Her family history did not reveal any reliable conspicuous findings related to either MRKHS or HOS. At the age of 6 months, the patient underwent surgical correction of a congenital APW. She also had skeletal disorders as described below. At the age of 11, pubic hair growth began, and her thelarche was obvious when she was 12 years old. Despite normal development of secondary sexual characteristics, she failed to menstruate. Surgical intervention for bilateral inguinal hernia was performed when she was 20 years old. She has suffered from asthma since the age of 16. At the age of 18, she noticed that she was unable to have sexual intercourse.

Upon presentation, the patient was 1.54 m tall and weighed 47 kg. On physical examination, musculo-skeletal disorders were noticed as follows: scoliosis of the lumbar spine and weakness of the M.trapezius, M.deltoides and Mm.biceps and triceps. Abduction and opposition of the right thumb, which was in the same plane as the fingers, were impaired. She also had hypoplasia of the left humerus with absence of radius and ulna (phocomelia, Figure 1). Her breast development was normal, Tanner 5, as was that of her pubic hair and her external genitalia. Instead of a normal vagina there was a small pouch 2 cm in length (Figure 2). Rectal palpation failed to detect a uterus, which was confirmed on transabdominal ultrasound examination. There was a normal female karyotype, 46,XX. Laboratory testing demonstrated normal levels of estradiol, testosterone and FSH.

The ECG revealed an incomplete right bundle branch block. Transthoracic echocardiography with colour-flow Doppler showed a mild ectasia of the aorta. Chest X-ray showed a hypoplastic left clavicle with the typical clavicular hook and bilateral hypoplastic third rib. Computed tomography of the abdomen demonstrated the absence of the uterus, while an intravenous pyelogram showed no abnormalities of the urinary tract.

The psychosexual identity of the patient is clearly female. She has a partner, and the impossibility of having sexual intercourse caused her great problems. After detailed information about the different options for creating a neovagina, the patient decided to undergo laparoscopic creation of a neovagina by the modified Vecchietti method. Intraoperatively, rudimentary uterine horns were identified adjacent to the morphologically normal ovaries which were located at the pelvic side walls. Surgery and the post-operative course were uneventful, resulting in a neovagina 10 cm in length.

Discussion

To the best of our knowledge, this is only the second report on the concurrence of MRKHS and HOS (Fakih et al., 1987), and the first case of HOS with APW in the scientific literature (literature review by MEDLINE search). The patient reported in the paper by Fakih et al. (1987) was a 15-year-old Caucasian female with a normal 46,XX karyotype who presented with absent uterus and vagina (Rokitansky syndrome), and an atrial septal defect which required closure when the patient was 5 years old. In addition to this cardiac defect, she also had skeletal malformations as follows: fusion of the middle and distal phalanx of the right little toe, presence of 13 thoracic vertebrae and ribs, and triphalangism of the right thumb with a middle phalanx. Both thumbs were in the same plane as the fingers (see our patient). Thus, the criteria for both Rokitansky syndrome and HOS were fulfilled (Fakih et al., 1987).

There are other hereditary and sporadic complex malformation syndromes concerning Mullerian anomalies, renal, heart and skeletal malformations that have been classified and separated from classical MRKHS, e.g. Klippel–Feil syndrome (KFS), MURCS association and VACTERL association. KFS was traditionally defined by the ‘classic triad’ of short neck, low posterior hairline and restriction of neck movement due to segmentation failure of the cervical vertebrae (Scott, 1993). The original definition of three types of KFS by Feil has been replaced by a new classification by Clarke. This classification is based on the inheritance and the most rostral vertebral fusion
diagnosed (Clarke et al., 1998). Other anomalies that are typical of KFS, such as spina bifida, Sprengel anomaly (30%) and deafness (30%), are not common in MRKHS. However, a unique family with KFS has been reported with hypoplasia of the thumb, one of the characteristic anomalies in MRKHS (Hensinger et al., 1974). The VACTERL association includes vertebral anomalies, cardiac and renal malformations and limb anomalies. The MURCS association is a combination of Müllerian duct aplasia, renal aplasia and cervicothoracic somite dysplasia. These syndromes are rare.

The absence of the vagina is a huge problem for the affected women. This diagnosis not only means infertility but also makes it impossible to have satisfactory vaginal intercourse. The laparoscopic creation of a neovagina by the modified Vecchietti technique is simple, safe and effective, with good functional results (Keckstein et al., 1995). In addition, having MRKHS and HOS may cause serious psychosexual and psychosocial problems. Therefore, sound knowledge concerning options as well as the limits of different therapeutic interventions is essential when counselling such patients. Psychological and social support is also needed. The large number of associated disorders of MRKHS and HOS is an interdisciplinary challenge facing cardiologists, cardiovascular and orthopaedic surgeons, and gynaecologists.

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