

OEIS complex (omphalocele-exstrophy-imperforate anus-spinal defects) in monozygotic twins: a case report and literature review

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Summary

The omphalocele-exstrophy-imperforate anus-spinal defects (OEIS) complex represents severe midline abdominal and pelvic defects of unknown etiology. This complex is rare, affecting 1 in 200,000 to 400,000 pregnancies and is extremely rare in twin or triplet gestations. Here, we report the OEIS complex in a spontaneous monozygotic twin pregnancy and previously reported OEIS complex in twin or triplet pregnancy are reviewed. Spontaneous pregnancy and unremarkable family history, but concordance of monozygotic twins for the defect may support the theory that early malformation complexes, e.g., OEIS, may be related to errors in monozygotic splitting in early blastogenesis.

Key words: Omphalocele-exstrophy-imperforate anus-spinal defects (OEIS); Twin pregnancy.

Introduction

The OEIS complex, also known as the exstrophy of the cloaca, is an acronym for omphalocele, exstrophy of the bladder, imperforate anus and spinal defects. These uncommon congenital anomalies were initially described by Carey *et al.* [1]. He and his colleagues proposed the OEIS complex following a series of cases with abnormal body wall development [1]. Subsequently, additional malformations were reported to be associated with the OEIS complex in addition to the four classic malformations (omphalocele, exstrophy of the cloaca, imperforate anus, and spine abnormalities), and included genital abnormalities, renal malformations, symphysis pubis diastasis, and limb abnormalities [2].

The incidence of OEIS complex ranges from 1/200,000 to 1/400,000 and most cases of OEIS complex occur spontaneously [1, 3, 4]. Due to the rarity of this disease, the etiology of OEIS complex is unclear. Only a few cases have been reported in twin and triplet gestations (Table 1) [5-29]. Here we report monozygotic twins concordant for OEIS complex. Its phenotype without genetic defects might support the theory that a splitting error in monozygotic gestations is related to the occurrence of OEIS complex.

Case presentation

A 21 year-old woman (gravida 1, para 0) with a monozygotic twin pregnancy, was referred to our maternal and fetal unit for detailed ultrasonographic examination due to multiple fetal malformations. The parents were healthy and non-consanguineous, and their family histories were non-contributory to multiple pregnancies and OEIS complex. The fetuses were spontaneously conceived without in vitro fertilization (IVF) treatment. The pregnancy was uncomplicated, with no maternal diabetes, infections, or exposure to teratogens. Ultrasonography had been performed at another hospital at 10 weeks gestation and demonstrated a monochorionic monoamniotic twin pregnancy on a sonographic report without images. Detailed ultrasonography at our maternal and fetal unit was performed. Firstly, a single placenta was located posterior to the uterus and two fetuses shared an amniotic sac. Ultrasound examination revealed similar findings in twin A and B with an estimated gestational age of 15 weeks (Fig. 1a). They both had gastroschisis, scoliosis, myelomeningocele, a single umbilical artery and short umbilical cord. The prenatal diagnosis was limb body wall defect (LBWD).

Amniotic fluid samples were obtained from amniocentesis under ultrasonic guidance, and the amniotic fluid cells were cultured for one week, followed by G-banding karyotyping analysis using a Metascan Karyotyping System (Imstar S.A., Paris, France). The chromosomal phenotype of the twins was 46XY. Simultaneously, chromosomal microarray analysis using a 44K Agilent array showed normal chromosomes. The family decided to terminate the pregnancy after consulting an obstetrician and pediatrician due to the poor prognosis of LBWD. An abortion was carried out at another hospital and the abortus (A and B) was sent to us for post-mortem examination. We were unable to obtain the placenta. We contacted the delivery doctor by cell phone and were told that a single placenta was observed in the twin pregnancy.

On post-mortem examination of twin A, the abortus weighed 168 g and the crown-rump length was 10 cm. A large abdominal wall defect was present (Fig. 1b). Protruded through this abdominal defect were the liver, spleen, stomach, intestines, kidneys, and urinary bladder. No anal opening was identified; the external genitalia were indeterminate with one small testis on each side of the perineum. In addition, kyphoscoliosis with a posterior sacral myelocystocele was shown on X ray film (Fig. 1c). Twin B had similar abnormalities to twin A, weighed 170 g and measured 9.5 cm crown-to-rump. The postnatal diagnosis for twin A and B was OEIS complex.

Discussion

During normal embryogenesis at the 4-week stage, a lateral infraumbilical mesoderm invades the cloacal membrane located on the anterior caudal end of the embryo. This invasion gives rise to the formation of the lower abdominal wall in combination with the growth of the urorectal septum, which separates the primordial urogenital sinus from the anorectum; these comprise the essential steps in the normal development of an early embryo [30]. With regard to the pathogenesis of OEIS complex, there are two remarkable assumptions among the many hypotheses. One hypothesis proposes that premature rupture of the cloacal membrane leading to failure of the invasion of the lateral mesoderm toward the anterior wall and division of the urogenital sinus from the anorectum may be the main cause of OEIS complex [31, 32]. The other hypothesis proposes that a defect in blastogenesis leading to abnormal mesodermal migration, may be the primary abnormality in OEIS complex [33, 34]. Although the original defect is arguable in the pathogenesis of OEIS complex, agreement concerning the cause of clinical presentation has been achieved due to the following reasons: 1) persistence of the cloaca with a rudimentary mid-gut and imperforate anus are due to failure of cloacal septation; 2) exstrophy of the cloaca, omphalocele, and lack of fusion of the pubic rami are caused by failure of the cloacal membrane to break down; and 3) abnormal ver-

Table 1. — *The reported 30 cases of OEIS complex in twins or triplets*

Case No.	Study	Year	Zygozity	Concordance
1	Koffler et al. [5]	1978	monozygotic	discordant
2	Schinkel et al. [6]	1979	monozygotic	discordant
3	Ornoy et al. [7]	1980	monozygotic	discordant
4	Nance [8]	1981	monozygotic	discordant
5	Redman et al. [9]	1981	monozygotic	concordant
6	Lowry and Baird [10]	1982	Not reported	concordant
7			monozygotic	concordant
8	Hesser et al. [11]	1984	Not reported	discordant
9	Langer et al. [12]	1992	monozygotic	discordant
10	Chitrit et al. [13]	1993	monozygotic	concordant
11	Kapur et al. [14]	1994	monozygotic	concordant
12	Meizner et al. [15]	1995	monozygotic	discordant
13			monozygotic	discordant
14	Bruch et al. [16]	1996	dizygotic	discordant
15	Pinette et al. [17]	1996	Not reported	discordant
16	Goldfischer et al. [18]	1997	monozygotic	concordant
17	Kramer et al. [19]	1997	monozygotic	concordant
18	Lee et al. [20]	1999	monozygotic	concordant
19	Shanske AL et al. [21]	2003	trizygotic	discordant
20	Siebert et al. [22]	2005	monozygotic	concordant
21	Noack et al. [23]	2005	dizygotic	concordant
22	Ben-Neriah et al. [24]	2007	dizygotic	discordant
23			monozygotic	concordant
24	Keppler-Noreuiletal. [25]	2007	monozygotic	discordant
25			Not reported	discordant
26			Not reported	discordant
27	Yokoyama E et al. [26]	2007	trizygotic	discordant
28	Tiblad et al. [27]	2008	Monozygotic	discordant
29	Mathew R et al. [28]	2009	monozygotic	discordant
30	Kunapinun N et al. [29]	2017	monozygotic	discordant



Figure 1. — Figures of twins. (a): Twin A and B with an estimated gestational age of 15 weeks on ultrasonographic image. (b): Post-mortem examination showing a large abdominal wall defect in twin A and B. (c): Kyphoscoliosis of twin A and B on X ray film.

tebrae in which there is protrusion of the dilated spinal cord (hydromyelia) and a cystic, skin covered mass in the lumbosacral region arise from the lumbosacral somites [20].

In our case, twins A and B showed the presence of an omphalocele, exstrophy of the cloaca, imperforate anus and spinal bifida which was categorized as classic OEIS complex [35]. With regard to the additional malformations of genitourinary anomalies, skeletal anomalies, and a single umbilical artery, these are usually reported in association with OEIS complex [20, 25]. A prenatal diagnosis of OEIS by ultrasound is possible, but the differential diagnosis between LBWC and OEIS complex is challenging in some cases. In this case, sonography displayed gastroschisis, scoliosis, myelomeningocele, a single umbilical artery, short umbilical cord, and the diagnosis of LBWC was suspected. The reason for the misdiagnosis was due to the short cord that is usually present in phenotype II LBW complex [36] and rupture of the omphalocele sac, which is unusual in OEIS complex. Similar misdiagnoses due to these same reasons were reported by Lee in twins [20]. Based on his findings, he proposed that OEIS complex with a short cord may represent part of the spectrum of LBW complex. More recently, OEIS fetuses with absence of umbilical cord were reported by Mandrekar [37], and his case further supported the theory that OEIS and LBWC represent a continuous spectrum of abnormalities rather than separate conditions. Thus, in some cases, the diagnosis of OEIS should not be made until postnatal surgery or autopsy is carried out as in our case.

A higher incidence of the OEIS complex has previously been reported in twins and triplets. As summarized in Table 1, in the English literature we found that OEIS (cloacal exstrophy) has been reported in 28 sets of twins and 2 sets of triplets, including 20 monozygotic, 3 dizygotic, 2 trizygotic and 5 sets of unknown zygosity. Of the 20 monozygotic twins, the anomalies were concordant in 9 sets and discordant in 11 sets. On the one hand, the higher incidence of OEIS in monozygotic twins than in dizygotic twins suggests a possible genetic contribution to the occurrence of

these defects. On the other hand, the fact that discordance was more frequent than concordance whether in twins or triplets, seems to indicate that the gene does not play a role in the OEIS complex. There are two explanations for the concordance rate in monozygotic twins being well below 50%. The first is that a concordant twin is aborted early in pregnancy and the loss can obscure a strong connection with twinning [8]. The other explanation is that the opportunities for asymmetry, cytoplasmic deficiency, and competition during the twinning process may benefit the discordant expression of midline neurological defects in twins such as the OEIS complex [20]. Recently, Fullerton BS *et al.* observed that approximately 14% of all cases of cloacal exstrophy occurred in the same-sex twins [38] and their findings supported the hypothesis that the embryogenesis of cloacal exstrophy may be related to errors in monozygotic splitting, which was first proposed by Schinzel [6].

The etiology of OEIS complex has not been described, but appears to be heterogeneous. Most cases are sporadic without obvious etiology. It has been suggested that single gene defects may give rise to the OEIS complex [1]. For example, Nye *et al.* [39] described a case of myelocystocelo-cloacal exstrophy associated with a mitochondrial 12SrRNA mutation, which was previously reported to cause aminoglycoside-induced deafness. It has also been suggested that homeobox genes such as HLXB9 and retinoic acid or its receptor may play a role in the OEIS complex [40]. Recently, with the advancement of genetic technology, an increasing number of chromosomal anomalies have been reported to be associated with the OEIS complex, such as a 9q34.1-qter deletion, 3q12.2-3q13.2 deletion, 1p36.33-p36.32 deletion, etc. [41, 42, 43, 44], but these associations have been limited to one or two cases and sufficient evidence is lacking. In contrast, in 13 patients with OEIS complex, disease-causing mutations whether in candidate genes or the whole chromosome, have not been identified [45]. Similarly, our case showed a normal karyotype without chromosomal abnormalities on chromosomal microarray analysis.

In summary, we describe a set of twins concordant for OEIS complex without genetic defects, in which the OEIS complex was misdiagnosed prenatally as LBWD. The concordance of monozygotic twins for this complex may support the theory that early malformation complexes, e.g., OEIS, may be related to errors in monozygotic splitting in early blastogenesis.

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Conflict of interest

There is no conflict of interest to declare.

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