

SYNDROMES AND DISORDERS ASSOCIATED WITH OMPHALOCELE (II): OEIS COMPLEX AND PENTALOGY OF CANTRELL

Chih-Ping Chen*

Departments of Obstetrics and Gynecology, and Medical Research, Mackay Memorial Hospital, Taipei, Department of Biotechnology and Bioinformatics, Asia University, and College of Chinese Medicine, China Medical University, Taichung, Taiwan.

SUMMARY

Omphalocele-exstrophy-imperforate anus-spinal defects (OEIS) complex is characterized by a combination of omphalocele, exstrophy of the bladder, an imperforate anus, and spinal defects. Pentalogy of Cantrell is characterized by a combination of a midline supraumbilical abdominal wall defect, a defect of the lower sternum, a defect of the diaphragmatic pericardium, a deficiency of the anterior diaphragm, and congenital cardiac anomalies. This article provides a comprehensive review of OEIS complex and pentalogy of Cantrell, including the pathogenesis, prenatal diagnosis, differential diagnosis, and associated malformations. Omphalocele is an important sonographic marker for OEIS complex and pentalogy of Cantrell. Prenatal detection of an abdominal wall defect associated with multiple midline defects should alert one to the possibility of OEIS complex and pentalogy of Cantrell and prompt the genetic investigation and counseling of the disorders. [*Taiwan J Obstet Gynecol* 2007;46(2):103–110]

Key Words: OEIS complex, omphalocele, pentalogy of Cantrell

OEIS Complex

OEIS complex (OMIM 258040) arises from a single localized defect in the early development of the mesoderm that will later contribute to infraumbilical mesenchyme, cloacal septum and caudal vertebrae. The incidence of OEIS complex has been reported to range between 1/200,000 and 1/250,000 live births [1]. OEIS complex, which has a variety of other terminologies such as ectopia cloacae, vesicointestinal fissure, exstrophiasplanchica, and cloacal exstrophy, was named by Carey et al to describe the combination of omphalocele, exstrophy of the bladder, an imperforate anus, and spinal defects (Figures 1 and 2) [2]. This multisystem malformation represents the most severe form of the

exstrophy-epispadias sequence ranging from phallic separation with epispadias, pubic diastasis, bladder exstrophy, cloacal exstrophy to OEIS complex. Most cases of OEIS complex occur spontaneously, but there are reports of recurrence in siblings and concurrent occurrence in monozygotic twins, suggesting a genetic contribution to the pathogenesis of OEIS complex [3]. OEIS complex or cloacal exstrophy has been shown to be associated with prenatal exposure to diazepam, Opitz G/BBB syndrome, Goltz syndrome, trisomies 13, 18 and 21, triple X syndrome, oculoauriculovertebral syndrome, frontonasal dysplasia, mutations in mitochondrial 12S rRNA, and mutations in homeobox genes such as *HLXB9*, 3q12.2–q13.2 deletion, and 9q34.1–qter deletion [2,4–12]. Maternal α -fetoprotein is elevated in OEIS complex. Prenatal diagnosis of OEIS complex can be made by ultrasound. The characteristic sonographic findings of OEIS complex include omphalocele, lumbosacral myelomeningocele, nonvisualization of the bladder and external genitalia, and limb defects such as clubfeet or a missing lower limb [8,13–25]. Meizner and Bar-Ziv first reported the prenatal diagnosis of

*Correspondence to: Dr Chih-Ping Chen, Department of Obstetrics and Gynecology, Mackay Memorial Hospital, 92, Section 2, Chung-Shan North Road, Taipei, Taiwan.
E-mail: cpc_mmh@yahoo.com
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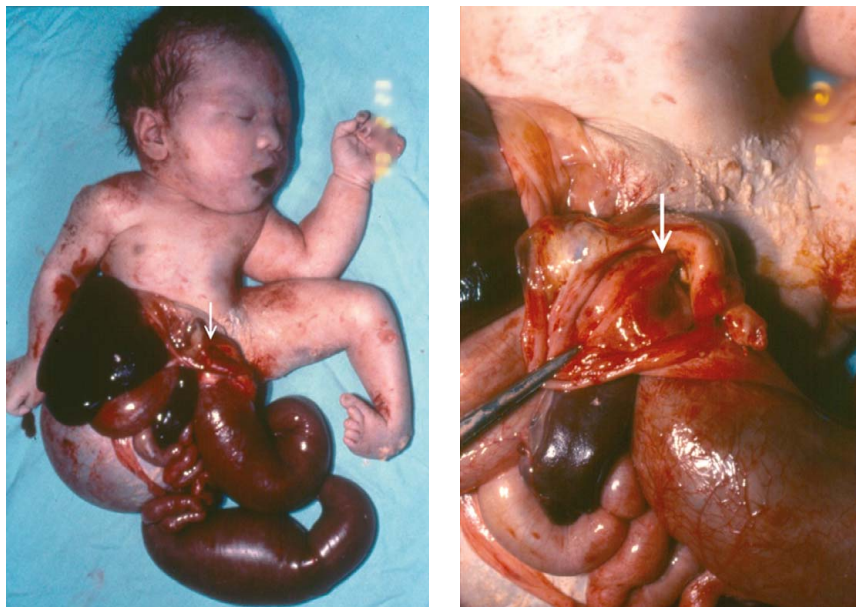


Figure 1. Anterior view of an infant with OEIS complex. Arrows indicate exstrophy of the bladder.

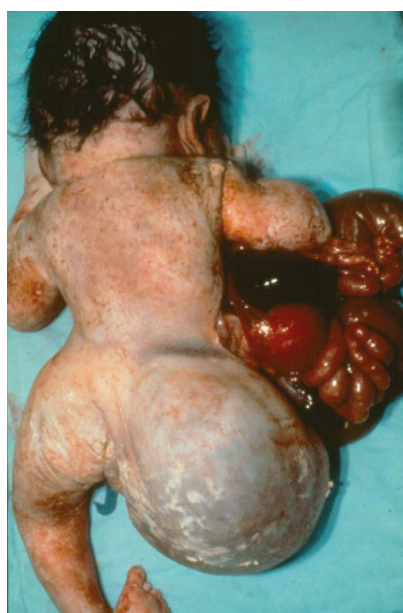


Figure 2. Posterior view of an infant with OEIS complex shows myelomeningocele and a deficiency of the lower limb.

OEIS complex by ultrasound in the third trimester [14]. Kutzner et al first reported the second-trimester sonographic diagnosis of OEIS complex [15]. Girz et al first reported the first-trimester sonographic diagnosis of OEIS complex [16]. Chen et al documented the perinatal features of two cases of OEIS complex associated with omphalocele, a large meningomyelocele, and severe limb defects [17]. The authors emphasized that an accurate prenatal diagnosis of OEIS complex and the associated malformations is important for the detailed counseling of the family as well as appropriate perinatal management. Schemm et al first reported the

association of OEIS complex with increased nuchal translucency [18]. Wu et al suggested that color Doppler sonography for identifying the perivesical umbilical arteries is a useful method in the prenatal diagnosis of OEIS complex [19]. Witters et al reported the prenatal manifestations of a mild form of OEIS complex without bladder exstrophy but with persistent urachus, and an anogenital malformation with ambiguous genitalia [20]. Shanske et al reported OEIS complex in a triplet pregnancy after *in vitro* fertilization and chorionic villus sampling [21] and suggested a uterine vascular pathogenesis of OEIS complex in humans. Vasudevan et al used postmortem magnetic resonance imaging (MRI) to study the structural anomalies of infants with OEIS complex [23]. Chen et al used fetal tomographic ultrasound imaging (TUI) and MRI for the prenatal diagnosis of OEIS complex in a fetus at 20 gestational weeks and suggested that fetal TUI and MRI are useful adjuncts to conventional two-dimensional ultrasound in the prenatal diagnosis of OEIS complex [25]. Fetal MRI is helpful for obstetricians in making a correct diagnosis to provide accurate information of the structural defects of the cloaca, the spinal defect, the abdominal wall defect, and the pathologic status of the bowels. Fetal TUI helps to produce a series of tomographic images for the prenatal delineation of the anatomic structures of the complex malformations and the abnormal vasculature of the umbilical artery.

Differential diagnosis of OEIS complex includes amniotic band sequence (ABS), body stalk anomaly, pentology of Cantrell, limb-body wall complex (LBWC), and human homologue of the mouse mutant *Disorganization* (*Ds*) gene [21,23]. ABS consists of a group of sporadic

abnormalities characterized by congenital ring constrictions or amputation of the digits and limbs, terminal digital fusion (pseudosyndactyly), talipes, and multiple craniofacial, visceral and body wall defects. Cranial defects associated with ABS include hydrocephalus, microcephaly, asymmetric encephalocele, meningocele, exencephaly, acrania, acalvaria, and anencephaly. Facial anomalies include cleft lip (usually bilateral), bizarre midfacial clefts, nasal deformity, bony orbital clefts, hypertelorism, eyelid colobomas, ptosis, ectropion, lacrimal outflow obstruction, and corneal opacities. The ABS is usually a sporadic event, although a few reported cases have been associated with teratogens such as methadone and lysergic acid diethylamide [26]. Familial ABS is due to hereditary connective tissue abnormalities such as Ehlers-Danlos syndrome type IV, and osteogenesis imperfecta [26].

The body stalk anomaly is characterized by a large abdominal wall defect, a short umbilical cord, and other abnormalities such as sharp angulation of the spine, but is not associated with craniofacial malformation or limb anomaly [27,28]. There is a phenotypic overlap between body stalk anomaly and LBWC. The possible pathogenesis of body stalk anomaly includes severe maldevelopment of body folds when the trilaminar embryo is transformed into the cylindrical embryo [27], and mechanical teratogenesis following rupture of the chorion or yolk sac [29].

Pentalogy of Cantrell consists of a specific combination of congenital defects with the full pentalogy consisting of a midline supraumbilical abdominal wall defect, a defect of the lower sternum, a defect of the diaphragmatic pericardium, a deficiency of the anterior diaphragm, and congenital cardiac anomalies [30].

The LBWC describes a heterogenic group of fetal malformations including lateral body-wall defects and limb reduction anomalies [31–38]. Cases of LBWC with craniofacial defects frequently show severe anomalies of the upper limbs, craniofacial defects, constrictive amniotic bands, and cranioplacental attachment, whereas cases of LBWC without craniofacial defects usually present major anomalies of the lower limbs, abnormal genitalia, anal atresia, renal defects, abdominoplacental attachment, and umbilical cord abnormalities [38,39]. The difference in the incidence of births between these two groups may be due to the different pathogenesis or the lethality causing early pregnancy loss in cases of LBWC with craniofacial defects [38]. The pathogenetic theories of LBWC include early amnion rupture [40], vascular disruption [31,32], and early embryonic maldevelopment [41,42]. Russo et al suggested that LBWC with craniofacial defects is caused by an early vascular disruption, whereas LBWC without craniofacial defects

is related to a defective lateral and caudal folding process of the embryonic disk [39].

Birth defects resembling those caused by the mouse mutant *Ds* gene (i.e. *Ds*-like human malformations) include both the common human birth defects, e.g. neural tube defects, orofacial clefting, gastroschisis, and limb defects, and the rare ones, e.g. anophthalmia and duplicated rectum [43]. In mice with *Ds* mutations, the defects involve duplications, aplasia or atresia, malformations, malposition, retention of embryonic structures, and hamartomas. Many *Ds*-like human malformations have been reported [43]. A comparison of anomalies associated with OEIS complex, LBWC and *Ds*-like human malformations is given in the Table [21,38,39,43].

The prognosis for OEIS complex is almost always fatal, and complex genitourinary surgery with unfavorable outcome should be included in the perinatal counseling [23,24,44].

Thoracoabdominal Syndrome

Thoracoabdominal syndrome (TAS; OMIM 313850) is characterized by X-linked midline defects that include diaphragmatic and ventral hernias, hypoplastic lungs, and cardiac anomalies. Pentalogy of Cantrell is also an X-linked disorder and consists of five associated anomalies: a midline epigastric abdominal wall defect, a defect of the lower sternum, a defect of the anterior diaphragm, a defect in the diaphragmatic pericardium, and intracardiac defects. High or supraumbilical omphalocele is usually a primary finding in pentalogy of Cantrell. Carmi et al mapped the TAS gene to the region of Xq25–q26.1 between the DXS425 and HPRT loci [45]. Parvari et al further narrowed the region of the TAS gene to an interval about 2.5 Mb in the region of Xq25–q27 [46,47].

Pentalogy of Cantrell

The incidence of pentalogy of Cantrell has been estimated to be 1/65,000 live births [32]. Cantrell et al first described a specific combination of congenital defects with the following full pentalogy: (1) a midline supraumbilical abdominal wall defect; (2) a defect of the lower sternum; (3) a defect of the diaphragmatic pericardium; (4) a deficiency of the anterior diaphragm; and (5) congenital cardiac anomalies (Figure 3) [30]. The incomplete expression of the syndrome is well recognized, and the full pentalogy is a rare occurrence. With the advent of ultrasonography, prenatal diagnosis of pentalogy of Cantrell is now possible in the first trimester of pregnancy using two- and three-dimensional ultrasound

Table. Comparison of anomalies associated with OEIS complex, LBWC or *Ds*-like human malformations

Anomalies	OEIS complex	LBWC with CF defects	LBWC without CF	<i>Ds</i> -like malformations
CNS	Spinal defects, neural tube defects, meningocystocele	Encephalocele or exencephaly always associated with facial clefts, amniotic bands or adhesion between cranial defect and placenta	Meningocele, scoliosis	Anencephaly, encephalocele, meningomyelocele
Digestive system	Imperforate anus	Normal	Anal atresia	Intestinal duplication, imperforate anus
CF anomalies	None	Facial clefts, acranium or hydrocephalus	None	Micrognathia, frontonasal malformation, facial clefts
Sense organs	None	Ocular, nasal and/or auditory deformities due to cranioplacental attachment	None	Microphthalmia, anophthalmia, microtia
Trunk	Low-lying umbilicus, omphalocele	Abdominal wall defect, normal umbilical cord	Abdominal wall defect, anal atresia, persistent extraembryonic coelom, short cord	Gastroschisis, abdominal wall defect
Urogenital organs	Cloacal exstrophy, epispadias, divided phallus, renal agenesis	Normal	Primitive cloaca, absent bladder, abnormal external genitalia	Bladder exstrophy, bladder duplication, duplicated genitalia
Limbs/girdles	Pubic diastasis, malpositioning, agenesis, hypoplasia, atrophy with popliteal web, clubfeet or a missing lower limb	Upper limb anomalies	Lower limb anomalies, leg attached to lumbosacral junction	Limb duplication or reduction, amputation

OEIS = omphalocele-exstrophy-imperforate anus-spinal defects; LBWC = limb-body wall complex; CF = craniofacial; *Ds* = Disorganization gene; CNS = central nervous system. Adapted and modified from Russo et al [39], Robin et al [43], Shanske et al [21] and Chen et al [38].

by visualization of an ectopia cordis associated with an anterior abdominal wall defect [48–50]. Three-dimensional ultrasound in the third trimester has been reported to be useful for the assessment of structural malformations associated with pentalogy of Cantrell [35,51]. Fetuses affected with pentalogy of Cantrell may manifest fluid accumulation in the neck or chest. Markov et al [52] and Staboulidou et al [53] reported the association of pentalogy of Cantrell with increased nuchal translucency. Hsieh et al reported the first-trimester prenatal diagnosis of cystic hygroma in association with pentalogy of Cantrell in a fetus [54]. The accumulation of lymphatic fluid in the neck of fetuses affected with pentalogy of Cantrell may be caused by venous congestion due to cardiac displacement, associated cardiac defects, mediastinal compression

by the diaphragmatic hernia, or omphalocele [54]. Siles et al [55] and Desselle et al [56] reported the pre-natal sonographic finding of transient pericardial effusion in fetuses with pentalogy of Cantrell.

Cantrell et al suggested that the combination of five disorders be a specific entity and proposed an etiopathogenesis involving developmental failure of a segment of the lateral mesoderm at around 14–18 days of embryonic life [30]. The consequence is a failure in the development of the transverse septum of the diaphragm, and a failure in the ventromedial migration of the paired mesodermal folds of the upper abdomen. The heart and upper abdominal organs may protrude outside the proper cavities through the defect in the lower sternal region, and an abnormal development of the abdominal wall results in omphalocele. Expression



Figure 3. Pentalogy of Cantrell. Arrow indicates an ectopia cordis.

of the full pentalogy is rare. Incomplete expression and variants of the syndrome, however, are well recognized [57,58]. Various combinations of two or three of the five defects included in the pentalogy of Cantrell have been reported [59,60]. Carmi and Boughman suggested that pentalogy of Cantrell is associated with ventral midline defects resulting from an embryologic insult within the ventral midline developmental field [61]. The midline defects are confined to the ventral parts of the body, such as the abdominal wall, sternum, diaphragm, pericardium and heart. The combinations of these midline defects are likely to vary. Pentalogy of Cantrell is the most severe expression of anomalies in the ventral midline developmental field and is thought to be the result of mechanical teratogenesis [59], major gene mutations [45,47], chromosomal abnormalities, particularly trisomy 18 [62,63], and disruptive vascular defects [64].

Carmi and Boughman reported that both cleft lip with or without cleft palate and encephalocele tend to be especially associated with ventral midline anomalies within the spectrum of pentalogy of Cantrell [61]. Toyama [65], Spitz et al [66], and Ghidini et al [67] reviewed the literature and found that craniofacial malformations, such as anencephaly, meningocele, encephalocele and hydrocephalus, were associated with pentalogy of Cantrell. Other midline anomalies, such as sirenomelia [64], frontonasal dysplasia [68], exencephaly [58,69–71], and craniorachischisis [72], have also been reported to be associated with pentalogy of Cantrell. These reports support the proposal by Carmi and Boughman [61] that pentalogy of Cantrell is included among the defects of the midline

developmental field. Of note is the association of limb defects with pentalogy of Cantrell. TAS has been suggested as an X-linked dominant disorder [45]. Parvari et al mapped the TAS gene to Xq25–q27 and further narrowed the region of the gene to an interval of about 2.5 Mb [46,47]. The X-chromosomal split-hand/split-foot malformation (SHFM) has also been mapped to SHFM2 region at Xq26.3 [73,74]. Interestingly, TAS-associated limb defects have been described. Pivnick et al reported an infant with a midline TAS, a deficiency of the right lower limb, and ectrodactyly and suggested a possible mutation in the *Hox-4* genes [75]. Uygur et al reported an infant with pentalogy of Cantrell and limb defects diagnosed prenatally [76]. Chen et al reported a fetus with pentalogy of Cantrell, hypoplasia of the right upper limb, and ectrodactyly [77]. The cases reported by Pivnick et al [75], Uygur et al [76], and Chen et al [77] provide evidence for the concurrence of pentalogy of Cantrell and limb defects and imply a syndrome with involvement of the genes responsible for limb morphogenesis and fusion of the sternum.

Since defects of the midline developmental field are associated with aneuploidy, cytogenetic analysis is necessary at the time of prenatal diagnosis of pentalogy of Cantrell. Most patients and families tend to terminate the pregnancies because of the lethal nature of this anomaly. However, successful two-stage repair of tetralogy of Fallot associated with pentalogy of Cantrell has been reported [78], and one-stage repair of pentalogy of Cantrell is technically feasible [79]. Successful repairs of pentalogy of Cantrell by pediatric surgery may influence the perinatal management of affected fetuses with a normal karyotype.

Conclusion

This article provides a comprehensive review of OEIS complex and pentalogy of Cantrell, including the pathogenesis, prenatal diagnosis, differential diagnosis, and the associated malformations. Omphalocele is a prominent sonographic marker for OEIS complex and pentalogy of Cantrell. Prenatal detection of an abdominal wall defect associated with multiple midline defects should alert the clinician to the possibility of OEIS complex and pentalogy of Cantrell, and prompt the genetic investigation and counseling of the disorders.

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