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Prenatal Ascertainment of OEIS Complex/Cloacal Exstrophy—15 New Cases and Literature Review

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Omphalocele-exstrophy of the bladder-imperforate anus-spinal defects (OEIS) complex or cloacal exstrophy (EC), describes a rare grouping of more commonly occurring component malformations. The etiology is unknown, but likely heterogeneous. While postnatal identification of its associated gastrointestinal, spinal, and genitourinary systems delineates the extent and natural history of OEIS complex, prenatal findings may provide additional information regarding early detection, possible causative factors, and outcome. The purposes of this study were to: (1) present the prenatal ascertainment of OEIS complex in this series of 15 cases identified through several different sources compared to the literature, and (2) discuss the relationship of these prenatal findings to possible abnormal developmental mechanisms causing OEIS complex. These 15 cases indicate that OEIS complex may be difficult to diagnose prenatally, and that the full extent of abnormalities may not be clear until postnatal exam. Confusion with limb-body wall complex (two of our cases) and pentalogy of Cantrell (one of our cases) can occur. Anal/gastrointestinal malformations and genital ambiguity are under-ascertained. Conversely, prenatal defects may resolve postnatally, yet may provide clues for pathogenetic mechanisms. For instance, the finding of nuchal thickening in our three cases (one reported) suggests vascular/hemodynamic compromise early in embryologic development, or intrathoracic compression leading to jugular lymphatic obstruction may play a role. The association of twinning and OEIS complex suggests they may occur as early as blastogenesis. Our three sets of discordant twins also suggest a non-genetic etiology for OEIS complex of uteroplacental insufficiency. This study also indicates that OEIS complex may be more common than previously thought. © 2007 Wiley-Liss, Inc.

Key words: OEIS complex (omphalocele-exstrophy of the bladder-imperforate anus-sacral defects); cloacal exstrophy; prenatal findings

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INTRODUCTION

Omphalocele-exstrophy of the bladder-imperforate anus-spinal defects (OEIS) complex or cloacal exstrophy (EC), describes a rare grouping of more commonly occurring component malformations [Carey et al., 1978]. The etiology is unknown, but likely heterogeneous. While postnatal identification of its associated defects of the gastrointestinal, spinal, and genitourinary systems delineates the extent and natural history of OEIS complex, prenatal findings may provide additional information regarding early detection, possible causative factors, and outcome.

The purposes of this study were to: (1) present the prenatal ascertainment of OEIS complex in this series of 15 cases compared to the literature, and (2) discuss the relationship of these prenatal findings to possible abnormal developmental mechanisms causing OEIS complex.

METHODS

Fifteen cases with a diagnosis of OEIS complex having prenatal findings were identified through several sources. The medical records, including prenatal ultrasound reports, were reviewed for all the patients. Inclusion of cases was based upon the

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prenatal or postnatal presence of omphalocele with two of the other component features of OEIS complex (bladder exstrophy, imperforate anus, and spinal defects). These criteria were applied based upon other previous reviews of OEIS complex including those by Källén et al. [1999a, 2000], in which they found that the estimated probabilities for infants with at least two malformations within the OEIS complex to also have a third malformation within this group was 100% if the infant had omphalocele with bladder exstrophy, 68% if the infant had omphalocele with spine defects, and 69% if the infant had omphalocele with anal atresia. The probabilities of other combinations of two component defects of OEIS complex to have a third malformation were comparably high. All except one of our cases had three to four major component malformations of OEIS complex (omphalocele, exstrophy of the bladder, imperforate anus, and spinal defects), in addition to the other associated malformations involving the genitourinary and gastrointestinal systems and lower limb defects. Three had only a prenatal diagnosis without postnatal autopsy, while 12 of the 15 cases had postnatal identification of their defects through physical examinations and other diagnostic tests, and/or autopsy. Nine of the 12 cases were living at the time of their assessment; however two of the nine subsequently died soon after birth. Five of 15 cases were terminated.

Seven of 15 cases were ascertained through the University of Iowa Hospital & Clinics (UIHC) Fetal Diagnostic & Treatment Clinic database (2002–2006) based upon presence of omphalocele, ventral wall, spinal and/or bladder defects, or diagnosis of OEIS complex. Five of these seven cases were terminated. The birth rate for liveborns in Iowa has been 37,000–38,000/year, therefore, the estimated prevalence of OEIS complex for this period of time (2002–2006) including these terminations, would be approximately 1/27,174. Four additional cases were identified independently through the Iowa Registry of Congenital and Inherited Disorders (IRCID; 1984–2006). Four other cases with prenatal findings were identified and reviewed at The University of Michigan Medical Center in years 2002–2006. The birth rate is ~127,799 per year in Michigan; however, an estimated prevalence would not be accurate and would likely represent an under-ascertainment because these cases were selected and referred only from the Urology clinic at The University of Michigan. No cases of OEIS complex were identified from our University of Iowa Hospital & Clinics In Vitro Fertilization (IVF) and birth defects study of 1,805 cases (1,462 IVF-conceived, and 343 Intrauterine insemination (IUI)-conceived pregnancies) [Olson et al., 2005].

Reasons for referral for prenatal ultrasounds were: abnormal triple screen or maternal serum alpha-fetoprotein (MSAFP; n = 2) decreased fundal height growth (n = 1), gestational diabetes mellitus (n = 1), multiple anomalies seen on local ultrasounds (n = 4), myelomeningocele (MMC) with ventriculomegaly (n = 1), advanced maternal age (AMA; n = 1), abdominal wall defect versus abdominal cyst (n = 1), and cyst behind the neck and protrusion on abdomen (n = 1).

RESULTS

Prenatal ultrasound (12–25 weeks) identified a ventral wall defect in all 15 cases, omphalocele (11/15), bladder non-visualization (8/15), sacral mass, neural tube defect (NTD), or vertebral defects (10/15), lower extremity defect(s) (8/15), renal defects (6/15), ambiguous genitalia (3/15). The spine defects were described as abnormal curvature of the spine, protruding solid mass from lower sacrum, thoracic and lumbar scoliosis and kyphosis, abnormal shaped vertebrae, absence of the sacrum, and severe angulation of the spine. The lower extremity defects consisted of mostly of unilateral or bilateral clubfeet (n = 7), with one case having abnormal hyperextension at the knees. The renal defects were described as unilateral absence (n = 1), hydronephrosis (n = 1), hydroureter (n = 1), calyceal dilatation (n = 2), and ectopic kidney (n = 1).

Other findings in > or equal to 20% of cases were: increased nuchal translucency (3/15), growth retardation (4/15), two vessel cord (5/15), breech presentation (15–19 weeks) (3/15). Other findings in one or two patients included double-bubble sign consistent with duodenal atresia, malrotation, ascites (2/15), and diphallia. Imperforate anus and lung anomalies were not detected prenatally in any of the cases.

Table I presents the major prenatal findings in each case, including a summary of the number of the four key features of OEIS complex (omphalocele, bladder exstrophy, spine defects, imperforate anus). Prenatal detection of the four key features of OEIS complex in these cases was: 2/15 cases (13%) had only one of four of the findings, 8/15 cases (53%) had two of four of the findings, and 5/15 cases (33%) had three of four of the findings. None of the 15 cases had all four of the key findings. Although duodenal atresia and malrotation were identified prenatally, imperforate anus was not detected.

The diagnosis of OEIS complex was made or strongly suspected prenatally in 8/15 patients. However, the prenatal diagnoses of limb-body wall complex (two cases), pentalogy of Cantrell (one case) in a total of three patients were changed to OEIS complex after postnatal examinations were completed. In addition, five patients with omphalocele plus one or two additional abnormalities did not have a specific identified pattern of malformation described in the medical record.

TABLE I. Prenatal Findings in 15 Cases With OEIS complex

	Abdominal wall defect	Bladder exstrophy	Spine defects	Imperforate anus	Total # of four defects	Ambiguous genitalia	Other genitourinary defects	Limb defects	Twin	Other findings	Prenatal diagnosis
Case 1	+ (Non-specific)	+	+ (NTD T9-sacrum)		3/4		Calyceal dilatation	Clubfoot		Nuchal fold; HC	OEIS complex
Case 2	+	+ (Possible)			2/4		L absent kidney			2 VC; ↑ MSAFP	OEIS complex
Case 3	+ (Non-specific)	+ (Possible)	+ (NTD)		3/4					Nuchal fold	Prob. OEIS complex
Case 4	+		+ (T, lumbar, sacrum)		2/4					Nuchal cyst	NS
Case 5	+		+		2/4			B clubfeet	+	↑ MSAFP; 2 VC; Ascites	LBW complex
Case 6	+	+	+ (Spine mass = NTD)		3/4	+		R clubfoot		Nl MSAFP	OEIS complex
Case 7	+ (Non-specific)		+ (C scoliosis; T, lumbar angulation; mass in sacral region? teratoma)		2/4			L clubfoot; R hyperextended	+	↑ MSAFP; ascites	LBW complex
Case 8	+				1/4					2 VC	NS
Case 9	+	+			2/4	+	R renal pelvis and ureter dilated			2 VC; low MSAFP	OEIS complex
Case 10	+ (Possible thoracic-abdominal defect)		+		2/4						Pentalogy of Cantrell
Case 11	+		+ (MMC)		2/4		Perineal defect	B clubfeet		Ventriculomegaly	NS
Case 12	+	+			2/4				+	2 VC; abnormal triple screen	OEIS complex
Case 13	+	+	+ (MMC-possible lipomeningocele)		3/4		Male genitalia; ectopic kidney			Nl triple screen; Nl posterior fossa	NS
Case 14	+ (Possible)				1/4						NS
Case 15	+	+	+ (T scoliosis/kyphosis)		3/4		L hydronephrosis	B clubfeet			OEIS complex
Total	15/15	8/15	10/15	0/15		2/15	6/15	6/15	3/15		

+, Abnormal; L, left; Nl, normal; R, right; B, bilateral; NTD, neural tube defect; MMC, myelomeningocele; T, thoracic vertebra; C, cervical vertebra; HC, hydrocephalus; VC, vessel cord; ↑, elevated; Prob., probable; LBW, limb-body wall; NS, not stated.

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Table II presents the postnatal findings, outcome and diagnosis in the 15 cases. In all cases, the postnatal diagnosis was OEIS complex. Postnatal findings included: omphalocele in 15/15 cases (100%), bladder exstrophy 13/14 (93%), spine defects 15/15 (100%), and imperforate anus in 7/12 (58%). Other findings in > or equal to 50% of cases included genitourinary defects in 7/12 (58%) with 2/12 (17%) having ambiguous genitalia, clubfeet and other lower extremity abnormalities in 9/13 (69%), and other gastrointestinal defects in 6/12 (50%).

Prenatal histories included cigarette (n = 2), valproic acid (n = 1), and methamphetamine use (n = 2), obesity (n = 2), diabetes mellitus (n = 2), and multiple uterine fibroids (n = 1). Mean maternal age equaled 28 years; the oldest was at 35 years of age, and the youngest was at 17 years of age. MSAFP was elevated (n = 4), low (n = 1) and normal (n = 5). Three of 15 had an unaffected (normal) co-twin (one monochorionic, monoamniotic; two dichorionic, diamniotic). Chromosome analyses (12/15) were normal: 46,XX (n = 7), and 46,XY (n = 5).

Outcome of the 15 was termination in 5, and live births in 9 (two died within 1 hr of birth), and 1 stillborn. The cases that were terminated had no unique/different findings compared to the infants who were live births. There were no patients with evidence of urinary obstruction (or associated renal or pulmonary complications). Of the terminated cases, one was thought to have pentalogy of Cantrell on prenatal ultrasound studies, but on autopsy was diagnosed with OEIS complex. Three cases had increased nuchal translucency, and one had ascites, as did one of the infants who died at one hour of age.

DISCUSSION

These 15 cases and 20 reports in the literature indicate that OEIS complex/EC may be difficult to diagnose prenatally, and that the full extent of abnormalities may not be clear until postnatal exam [Gosden and Brock, 1981; Meizner and Bar-Ziv, 1985; Kutzner et al., 1988; Girz et al., 1998; Langer et al., 1992; Chen et al., 1997; Lee et al., 1999; Vasudevan et al., 2006]. Several authors have described major criteria for prenatal diagnosis of EC: non-visualization of the fetal bladder, infra-umbilical anterior abdominal wall defect, omphalocele, and MMC [Meizner and Bar-Ziv, 1985; Austin et al., 1998; Noack et al., 2005]. Minor criteria included: lower extremity malformations (clubfeet), renal anomalies, ascites, widened pubic arches, narrow thorax, kyphoscoliosis, hydrocephalus, and single umbilical artery [Girz et al., 1998; Källén et al., 2000; Noack et al., 2005].

However, despite these criteria, often the full extent of anomalies cannot be identified prenatally. As shown from comparison of our cases in Tables I and II, although all cases had the characteristic component findings of OEIS complex on postnatal examination, the majority had only two to three of four of these findings on prenatal studies. Imperforate anus/other anal defects and associated gastrointestinal anomalies, as well as genital ambiguity are under-ascertained prenatally, as seen in these cases of OEIS complex.

Confusion of OEIS complex with limb-body wall complex (two of our cases) and pentalogy of Cantrell (one of our cases) on prenatal ultrasound has been reported in the literature as well [Shanske et al., 2003]. It can be difficult to differentiate omphalocele and bladder exstrophy from other midline abdominal wall defects (gastroschisis, amniotic band sequence, and limb-body wall complex) [Lee et al., 1999; Wu et al., 2004; Noack et al., 2005]. Although the additional findings of a thoracic defect and absent spine defects may distinguish pentalogy of Cantrell from OEIS complex on prenatal ultrasound, these may not be appreciated [Noack et al., 2005]. Girz et al. [1998] and Wu et al. [2004] suggested use of color Doppler to depict urine flow in direct communication with abdominal cavity to detect bladder exstrophy and to show the course of the periumbilical arteries. Hamada et al. [1999] described an additional diagnostic ultrasound feature of "elephant trunk-like" image representing prolapsed terminal ileum, however, in another reported case this prenatal finding was identified postnatally as part of the external ambiguous genitalia [Witters et al., 2004].

These results indicate that prenatally diagnosed cases of omphalocele or an abdominal wall defect, if they had gone without a postnatal examination/autopsy, would have been unrecognized as having OEIS complex. Therefore, based upon these findings and those of other studies, it is likely that the incidence of OEIS complex is higher than reported, in part, because many cases are incorrectly diagnosed as isolated omphalocele, or another component defect [Hayden et al., 1983; Gosden and Brock, 1981; Petrikovsky et al., 1988; Chen et al., 1997; Lee et al., 1999].

Conversely, prenatal defects may resolve postnatally, yet they may provide information about pathogenetic mechanisms for some cases of OEIS complex. For instance, the finding of increased nuchal translucency/nuchal thickening was seen on prenatal ultrasound in three of our cases and in one reported case of OEIS complex [Schemm et al., 2003].

In general, increased nuchal translucency in chromosomally normal fetuses can be associated with a range of defects, most commonly cardiac, and with genetic syndromes; however the pathogenetic mechanisms are not known. Seventy-seven of 510 (or 15%) chromosomally normal fetuses with increased nuchal translucency had a congenital defect (combined data from several small series from Diploma in Fetal Medicine Series) [Nicolaides et al.,

TABLE II. Postnatal Findings in 15 Cases With OEIS complex

	Omphalocele	Bladder exstrophy	Spinal defect	Imperforate anus	Other GI defect	Other Genitourinary defect	Limb defect	CV defect	CNS defect	Lung defect	Outcome	Postnatal diagnosis
Case 1	+	+	+ (NTD)	NS	NS	NS	Clubfoot	NS	NS	NS	EA—no autopsy	OEIS complex
Case 2	+	Urethral atresia	+	+	Duodenal, colonic atresia; malrotation of small bowel	Diphallia; L absent kidney	Varus defect of feet	Nl	Nl	Nl	EA	OEIS complex
Case 3	+	+	+ (NTD)	NS	NS	NS	NS	NS	NS	NS	EA—no autopsy	OEIS complex
Case 4	+	NS	+	NS	NS	NS	NS	NS	NS	NS	EA—no autopsy	OEIS complex
Case 5	+	+	+ (Abnormal curvature, absent sacrum)	+	Duodenal atresia, malrotation	Didelphys uterus; hypoplastic kidneys	Clubfeet	Nl		Lobation abnl; hypoplastic	LB—died at 1 hr	OEIS complex
Case 6	+	+	+				R clubfoot				EA	OEIS complex
Case 7	+		+ (NTD, absent sacrum)		Malrotation liver cysts		Clubfeet; knee hyperextension		HC	Hypoplastic	LB—died at 1 hr	OEIS complex
Case 8	+	+	+	Abnormal perianal reflex		Patent urachus		CCHD (TGV, ASD, VSD, PS)			LB	OEIS complex
Case 9	+	+	+ (Tethered cord; intradural lipoma, syrinx)	+		Ambiguous genitalia; R hydronephrosis; L reflux			Nl	Nl	LB	OEIS complex
Case 10	+	+ (Possible)	+	+	Malrotation		B Talipes			Lobation abnl; hypoplastic	SB	OEIS complex
Case 11	+	+	+ (MMC)	+	Intestine duplication	Widely spaced labial folds (ambiguous); bifid uterus; vesicovaginal fistula	B clubfeet		Chiari malformation; HC		LB	OEIS complex
Case 12	+	+	+ (Terminale myelocystocele with tethered cord)	+		Nl female genitalia		PDA			LB	OEIS complex
Case 13	+	+	+ (Terminale myelocystocele)	+		Testes palpable in scrotum	Nl	Nl			LB	OEIS complex
Case 14	+	+		+	Rectovaginal fistula	Rectovaginal fistula	Vascular malformation of L leg	Nl	Nl		LB	OEIS complex
Case 15	+	+	+ (Tethered cord, abnormal sacrum)	+		Vaginal duplication; R hydronephrosis	B clubfeet	PDA			LB	OEIS complex
Total	15/15	13/14	15/15	7/12	6/12	7/12	9/13	1/12	2/12	3/12		

+, Abnormal; EA, elective termination; LB, live birth; D, died; Nl, normal; L, left; R, right; B, bilateral; NTD, neural tube defect; MMC, myelomeningocele; T, thoracic vertebra; C, cervical vertebra; HC, hydrocephalus; VC, vessel cord; ↑, elevated; Prob., probable; LBW, limb-body wall; NS, not stated; GI, gastrointestinal; CV, cardiovascular; PDA, patent ductus arteriosus; CNS, central nervous system; LE, lower extremity; SB, stillborn.

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1999] among which there were four cases of isolated omphalocele. Another study, The Fetal Medicine Foundation Project, evaluating 565 cases and 89 cases with detailed postnatal studies from a total of 4,116 pregnancies found 161 (3.9%) had structural defects and genetic syndromes, of which 7 had omphalocele, 2 with additional abnormalities of spina bifida and EC.

Based upon these studies in the literature, the prevalence of omphalocele and OEIS complex may be higher in fetuses with increased nuchal translucency than in the general population pointing to a probable association between OEIS complex and increased nuchal translucency. Furthermore, there may be a common cause(s) for increased nuchal translucency and OEIS complex. Several possible mechanisms include: (1) increased intrathoracic compression due to abdominal defects leading to jugular lymphatic obstruction, or (2) vascular or hemodynamic comprise early in embryologic development.

Prenatal ultrasound has allowed recognition of twin gestations making it clear that there is a higher reported incidence of OEIS complex in twins, the majority being monozygotic [Koffler et al., 1978; Redman et al., 1981; Smith et al., 1992]. This, in turn, suggests that both are manifestations of the same early disturbance of morphogenesis occurring as early as blastogenesis [Schinzel et al., 1979; McLaughlin et al., 1984]. Lee et al. [1999] reported one set of monozygotic twins concordant for OEIS complex and reviewed 18 other cases of OEIS complex in twins, consisting of 13 monozygotic (concordant in 3, discordant in 5, unknown in 5), 1 dizygotic, and 4 unknown zygosity. Two possible explanations for the concordance rate in monozygotic twins being below 50% include: loss of concordant twin may be aborted early in pregnancy, or that the twinning process with its inherent chances for asymmetry, cytoplasmic deficiency, and competition may favor discordant expression of midline defects, like OEIS complex [Nance, 1981].

A pathogenetic hypothesis for the association between cloacal anomalies and twinning is that the partial or complete duplication of the organizing center within a single embryonic disc may increase the risk of mesodermal insufficiency accounting for failure of complete development of the cloacal membrane and exstrophy [Siebert et al., 2005]. During later stages of gastrulation, the caudal eminence functions as a developmental field that is modulated by homeobox genes and a variety of other factors. Siebert et al. [2005] suggest that it is possible that the process of twin formation might disrupt the caudal eminence or its derivatives resulting in the defects seen in OEIS complex.

Our three sets of discordant twins along with other reports also suggest a non-genetic etiology for OEIS complex [Lee et al., 1999; Noack et al., 2005], including a uterine vascular pathogenesis. Several reports, including a report of EC in a fetus of a triplet/IVF pregnancy raised consideration of uteroplacental vascular insufficiency due to a single or additive factors: IVF, multiple gestation, trauma to the uterus or uterine vessels, placenta accreta or release of vasoactive substances from the placenta [Shanske et al., 2003].

CONCLUSIONS

This study indicates that MSAFP may not be a reliable screening test. Only 4/10 had elevated MSAFP (1 in a twin gestation). OEIS complex may be difficult to diagnose prenatally and may be more common than previously thought. The association of twinning and particular prenatal findings, such as increased nuchal translucency with OEIS complex/EC may provide insights into its pathogenesis.

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NOTE ADDED IN PROOFS

This study highlights the similarity of findings on prenatal ultrasound between OEIS and limb-body wall complexes. Recently, Heyroth-Griffis et al. [2007] reported cases having overlapping features of limb-body wall and OEIS complexes suggesting that these conditions may represent a spectrum of abnormalities. Based upon these observations, further discussion of the issue of a spectrum is warranted.

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