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CLINICAL CASE

Infrequent association of OEIS complex with a diaphragmatic defect

Asociación poco frecuente del complejo OEIS con un defecto diafragmático

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What do we know about the subject matter of this study?

OEIS complex is one of the most severe forms of presentation of abdominal midline malformations and involves several organs and systems. It has a favorable prognosis if there is a timely diagnosis and adequate correction with multidisciplinary management.

What does this study contribute to what is already known?

This study describes an OEIS complex in an unusual association with a diaphragmatic hernia. This occurrence could respond to a simultaneous presentation of the Cantrell pentalogy and the OEIS complex or a 1p36 deletion.

Abstract

Omphalocele-exstrophy-imperforate anus-spinal defects (OEIS) complex is a rare entity that presents abdominal wall defects, entails high morbidity and mortality, and requires multidisciplinary management. **Objective:** To describe a case with an unusual association between OEIS complex and diaphragmatic hernia and to discuss its pathogenesis and possible association with other midline malformations. **Clinical Case:** A preterm female newborn of 33 weeks of gestational age, with prenatal diagnosis of giant omphalocele that, at birth, presented intact amnion coverture containing the entire liver and some bowel loops, open bladder exstrophy and exposed urethral orifices; uterus didelphys, no palpable gonads, and concurrent imaging findings of pelvic soft tissue extrusion, left diaphragmatic hernia (Bochdalek), multiple bone defects, myelomeningocele, and myelocystocele. With these findings, OEIS complex with simultaneous presentation of Cantrell pentalogy or 1p36 deletion syndrome was suggested; in a genetic study chromosomopathies were ruled out but, a more specific study could not be performed. Colostomy, cloacal closure, and midline bladder plate closure

Keywords:
OEIS Complex;
Newborn;
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were performed, with adequate postoperative evolution. Given respiratory stability, surgical correction of the diaphragmatic hernia was delayed. After a long hospitalization, she was discharged and died due to intercurrent acute respiratory pathology. **Conclusion:** OEIS complex is a low prevalence entity and, within its clinical associations, diaphragmatic hernia is rare, which could correspond to an unusual form of the complex due to a simultaneous presentation of Cantrell pentalogy and 1p36 deletion syndrome. Despite being a sporadic malformation, it is important to know its characteristics and variations in order to perform an comprehensive multidisciplinary approach.

Introduction

The OEIS complex (OMIM 258040)[1] is a combination of defects comprising omphalocele, cloacal exstrophy, imperforate anus, and spinal defects[2]. While most cases are sporadic, familial cases have been reported with a higher incidence in monozygotic twins[3].

This is one of the most severe forms of abdominal midline malformations and includes characteristic defects involving the urinary, gastrointestinal, and musculoskeletal system, pelvic floor, abdominal wall, anus, and the spine. It is a rare variant of the bladder exstrophy-epispadias complex, with a variable clinical spectrum ranging from mild cases with isolated epispadias to severe cases with cloacal exstrophy. The form of presentation varies depending on the moment of embryological and fetal development when the alteration occurs[4]. It is a condition with high prenatal mortality and with a significant impact on postnatal quality of life in both patients and families[5].

The OEIS complex has an estimated prevalence of 1/82,000 to 1/250,000 live newborns[2], with a male-female ratio of 1:2[6]. Many cases are misdiagnosed prenatally as omphaloceles and isolated neural tube defects; other cases result in miscarriages and stillbirths, and a definitive diagnosis is achieved only at birth[7].

It is essential to differentiate the OEIS complex from other congenital alterations, such as megacystis, posterior urethral valves, permeable urachus with allantoic cyst, or amniotic band syndrome[4,5]. Among the associations described in the literature, diaphragmatic hernia is a rare and infrequent presentation of the OEIS complex. The objective of this work was to report a case with a rare association between OEIS complex and diaphragmatic hernia and to discuss its pathogenesis and possible association with other midline malformations.

Clinical Case

Preterm newborn of a second pregnancy of non-consanguineous parents, with a 27-year-old mother with no significant morbid history; 3 prenatal check-ups with diagnosis of omphalocele, but without follow-up; unknown personal, pathological, and toxic-allergic history and negative perinatal STORCH testing.

At birth, the newborn presented with undetermined sex, gestational age (GA) estimated at 33 weeks according to the Ballard test; weight 2300 grams, length 43 cm, head circumference 32 cm, anthropometric assessment of length/GA: -0.21 standard deviations (SD), weight/GA: +1.17 SD, and head circumference/GA: +1.11 SD; classified with weight and length appropriate for gestational age according to Intergrowth-21.

The initial physical examination showed a low anterior hairline, hypoplastic swallow, prominent ear lobes, broad nasal bridge, anteverted nostrils, left hemifacial microsomia, absence of the abdominal wall, giant omphalocele associated with bladder exstrophy, epispadias, no palpable gonads, imperforate anus, soft mass covered by skin at lumbosacral level, bilateral clubfoot, hypoplastic nails, triphalangeal thumbs, and broad hallux.

As the primary management, surgical correction of the omphalocele and ileostomy was performed through an exploratory laparotomy. At that time, a giant omphalocele-type defect of the anterior abdominal wall of approximately 12 cm was observed. It was centrally located, with an intact amnion containing the entire liver and some intestinal loops, associated with bladder exstrophy and exposed urethral orifices, uterus didelphys (each hemi-uterus with its respective tube and ovary), prolapse of around 15 cm of intestine through the cloaca, small intestine ending in the cecum and the latter in cloaca, with no evidence of the rest of the colon, in addition to pubic symphysis diastasis (figure 1 A and B).

Given these malformations, the study was completed with an echocardiogram that showed a 1-mm patent ductus arteriosus without hemodynamic repercussions, and severe pulmonary hypertension (65 mm hg). Imaging studies showed lower lumbosacral hemivertebrae, butterfly vertebrae at T9 and T12, hypoplastic iliac bones, and no visualization of the coccyx.

An abdominal CT scan showed a left diaphragmatic hernia (Bochdalek), with hypertrophy of the left hepatic lobe, causing anterior and inferior displacement

of the liver. This led to an abnormal position of the intestinal loops, which were oriented posteriorly and caudally, in addition to an ectopic gallbladder, right shift bladder with diffuse wall thickening, extrusion of the pelvic soft tissues, and bony malformations and myelomeningocele (figure 2 A and B). A brain MRI showed myelocystocele.

Based on these findings, a strong suspicion of OEIS complex with simultaneous presentation of pentalogy of Cantrell or 1p36 deletion was considered. The genetic study ruled out numerical and structural chromosomal abnormalities through G-banded 25 metaphases karyotyping, with results 46, XX.

As management, the pediatric surgery and urology group performed a colostomy, cloacal closure, and midline bladder plaque closure, with adequate postoperative evolution. Given respiratory stability during hospitalization, surgical correction of diaphragmatic hernia was deferred during this operative time, and it was considered to be performed later according to clinical evolution.

The hospital stay was prolonged; however, the patient was discharged with indication of outpatient multidisciplinary follow-up. Unfortunately, she died shortly after due to acute intercurrent respiratory pathology.

Discussion

OEIS complex can be suspected from the first and second trimester of pregnancy, initially as a large cystic mass in the lower abdomen while, in the second trimester, it can be found an increased nuchal translucency, vertebral abnormalities, spina bifida, and an umbilical cord with a single umbilical artery, suggestive of this entity[5]. The antenatal ultrasound of the patient showed omphalocele as the only significant finding.

The pathogenesis is not fully understood, but it is believed to be attributed to an alteration in the embryogenesis process which, under normal conditions, would lead to the urogenital and gastrointestinal system (cloacal tubercle) flowing into a common drainage structure known as cloaca by the fourth week of human embryonic development[5]. Between the fourth and seventh week of gestation, it divides into the urogenital sinus and the anorectal canal, thus forming the urorectal septum, which consists of mesenchyme that extends caudally through the cloaca towards the cloacal membrane with which they fuse in the seventh week of development, dividing the cloacal membrane into the urogenital membrane that will originate the bladder and prostatic urethra in males and the urethra and anterior part of the vagina in females, in addition to the anal membrane that will give rise to the anus and rectum. This membrane normally ruptures around the eighth week of development, creating anus and urogenital system passageways[5,8] but, in cases of OEIS, it is not generated in this way.

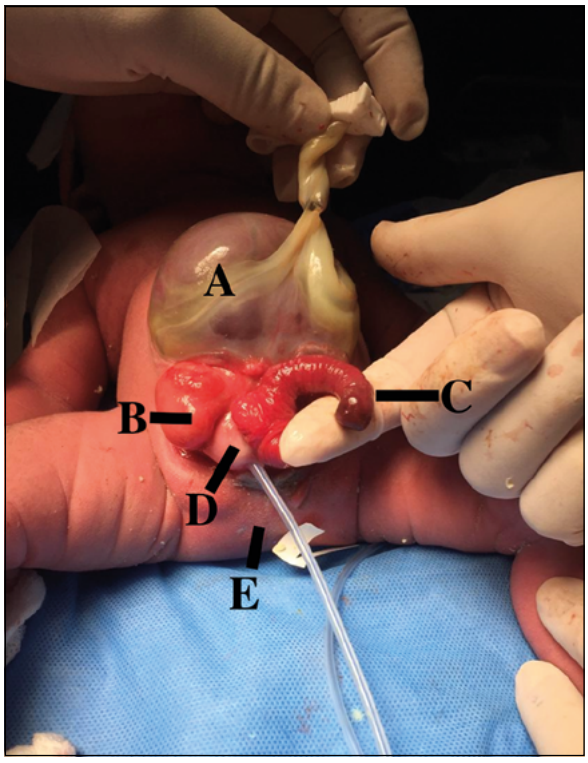

Figure 1 A. The following structures are shown A. Giant omphalocele (Anterior abdominal wall defect) with a length of approximately of 12 centimeters with an intact amnion covering the liver and some intestinal loops, B. Uterine body, C. Segment of intestine protruding as a blind loop, D. Bladder mucosa, bladder exstrophy and patent ureteral orifices, E. Imperforate anus.

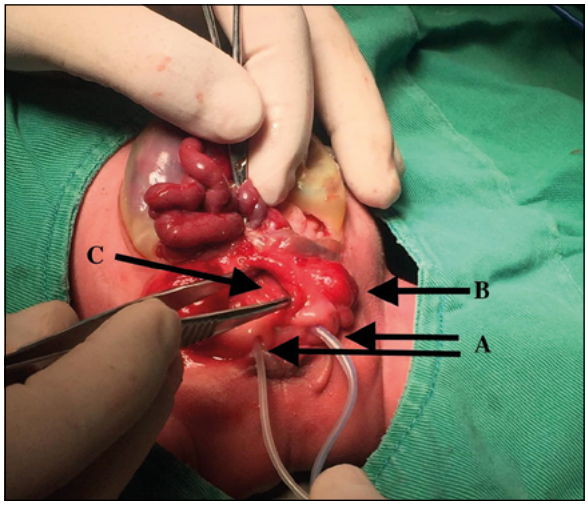

Figure 1B. The following structures are shown: A. Exposed and patent ureteral orifices, B. Uterine body, C. Cloaca

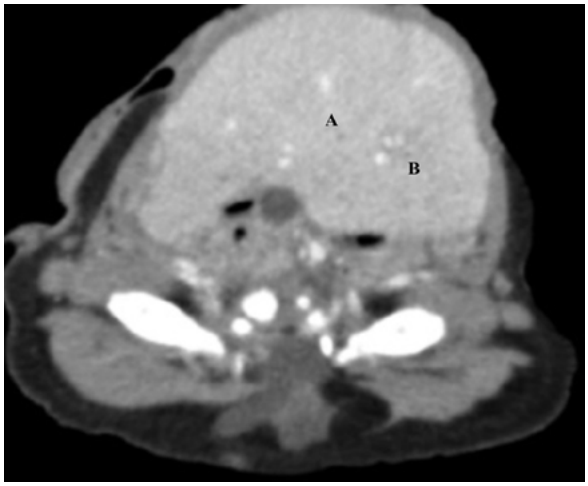

Figure 2 A. Abdominal computed tomography: transverse section showing A. Left diaphragmatic hernia (Bochdalek), B. Hypertrophy of the left hepatic lobe with displacement of the liver anteriorly and inferiorly, causing posterior and caudal displacement of intestinal loops.

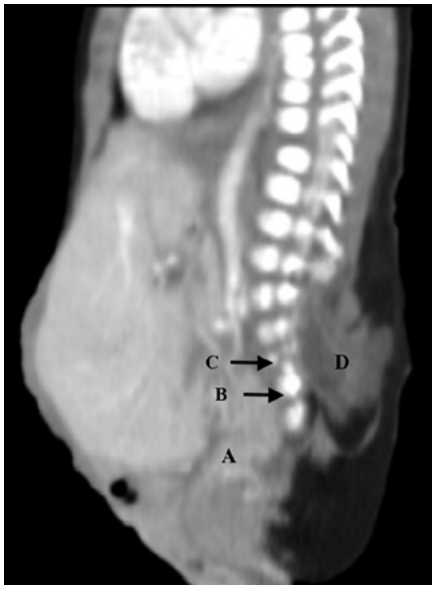

Figure 2B. Nuclear magnetic resonance of the spine and lumbosacral region, sagittal section showing: A. Extrusion of soft tissues in the pelvis, B. Dysplastic configuration of the sacrum, C. Sacral vertebral fusion defect and apparent coccyx agenesis, D. Meningomyelocele.

It is believed that a migration failure of the caudal mesenchyme is one of the main causes of this malformation since it would be responsible for the inadequate development of the infraumbilical mesoderm, the urorectal septum, and the lumbosacral somites[8]. The above-mentioned and the premature rupture of the cloacal membrane will cause a failure in the formation of the cloacal septum, producing a persistent cloaca and rudimentary hindgut with imperforate anus; all this will lead to an inadequate formation of the cloacal membrane, which will cause cloacal exstrophy, failure of fusion of the genital tubercles, and omphalocele as well as an alteration in the lumbosacral somites, generating an incomplete development of the lumbosacral vertebrae with hydromyelia[7,9].

Omphalocele is the most frequent and least variable malformation among the patients described[10], although there are also other relatively frequent malformations, such as absent uterus or uterus didelphys, as in the case presented; duplication of the urinary collecting system, renal agenesis, skeletal malformations such as rib anomalies, congenital hip dysplasia, thoracic hemivertebra, sacral anomalies, and/or clubfoot, which were also present in our patient. Myelocystocele is also reported, which accounts for 5% of lumbosacral masses and is common in patients with cloacal exstrophy; sexual developmental abnormalities are almost always present, with genital structures missing or varying degrees of ambiguity[8].

Among the associations described in the literature, the diaphragmatic hernia is a rare and infrequent presentation of the OEIS complex, however, it could correspond to an overlap with the pentalogy of Cantrell, which is a more severe expression of the developmental anomalies of the ventral abdominal midline, presenting defects in the supraumbilical abdominal wall, in the lower part of the sternum, and diaphragmatic pericardial defects as well as diaphragmatic hernia and congenital heart anomalies[11].

Both OEIS and pentalogy of Cantrell are defects that have a common embryological origin caused by a disruption between weeks 4-7 of embryological development as previously described, leading to a failure in the ventral folding of mesodermal cells that will form the thoracoabdominal wall, which could explain the presentation of diaphragmatic alterations in our patient[12].

In addition, it has been associated with chromosomal abnormalities such as trisomy 13, trisomy 18, and trisomy 21, as well as structural and chromosomal alterations such as 1p36 deletion, which could be another possible hypothesis for the presentation of this case[2]. This was first reported in 2009 by El-Hattab et al.[13], who found that the deleted region harbors approximately 70 genes and speculated that three of these may have possible contributing roles in the development of the OEIS complex. However, they concluded that there was no specific candidate gene and that the deleted region and phenotype could reflect a concurrent event. Later in 2016, Collus.M, et al.[14], presented the second patient with the same chromosomal anomaly associated with classical bladder exstrophy, diaphragmatic hernia, spina bifida, and

absence of the coccyx, supporting the possible role of genes in this region in the complex development of bladder exstrophy-epispadias, but they could not prove this hypothesis due to the lack of further genetic studies. Other chromosomal abnormalities that have been associated with the occurrence of this complex are 9q34.1 deletion and interstitial deletion of the long arm of chromosome 3.

In the case described, an in-hospital cytogenetic study was performed to rule out numerical and structural chromosomal abnormalities and, although it was necessary to extend the etiological study for microdeletion/microduplication or a monogenic syndrome, these could not be performed since the patient died after her discharge due to respiratory problems.

Other associated risk factors are maternal intake of drugs (diazepam, diphenylhydantoin, valproic acid, and increased intake of antacids), smoking, in vitro fertilization procedure, and radiation exposure[2,11]; none of these were identified in our case.

Regarding surgical treatment, this is a challenge due to the complexity of these malformations[15]. The first surgery for the correction of the OEIS complex can be achieved in single or staged procedures, and the goals include safe closure of the abdominal wall and bladder, preservation of renal function, prevention of short bowel syndrome, reconstruction of functionally and cosmetically adequate genitalia, and achievement of acceptable urinary and fecal continence[11]. Likewise, gender assignment is one of the first approaches that must be performed after the patient's stabilization since it influences the psychosocial adjustment and psychosexual development of the affected individuals, and early psychological support must be offered to their family and later to the patients[15,16].

In general, the prognosis is favorable after bladder reconstructive surgery, with approximately 80% of children achieving acceptable urinary continence rates[17]. If the final reconstruction is not successful, urinary diversion should be considered. At puberty, genital and reproductive function are important issues, although modern reconstruction techniques allow acceptable functionality and appearance. A full sexual life and having offspring represent the main indicators for successful genital rehabilitation, which is much easier to achieve in females than in males[11]. Finally, multidisciplinary follow-up in the first years of life will be indispensable for adequate rehabilitation after surgical procedures.

Conclusions

The OEIS complex is an entity of interest due to its infrequency and the need for comprehensive management by different pediatric specialties. There are very few descriptions in the literature that include left diaphragmatic hernia, as in the case presented, which could correspond to an unusual form of the complex due to simultaneous presentation with pentalogy of Cantrell or 1p36 deletion. Despite being a sporadic presentation malformation, it is important to know its characteristics and variants.

Ethical Responsibilities

Human Beings and animals protection: Disclosure the authors state that the procedures were followed according to the Declaration of Helsinki and the World Medical Association regarding human experimentation developed for the medical community.

Data confidentiality: The authors state that they have followed the protocols of their Center and Local regulations on the publication of patient data.

Rights to privacy and informed consent: The authors have obtained the informed consent of the patients and/or subjects referred to in the article. This document is in the possession of the correspondence author.

Conflicts of Interest

Authors declare no conflict of interest regarding the present study.

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