Egyptian Journal of Medical Human Genetics

REVIEW Open Access

Omphalocele: a review of common genetic etiologies

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Abstract

Omphalocele is one of the most common congenital defects in the anterior abdominal wall. The malformation is associated with various pathologies especially with chromosomal disorders. The developmental defect is observed in Congolese hospitals, but risk factors are not well precised on the published case reports, which are more often focused on management. We aim in this paper to make a review on the condition, insisting on the risk factors of omphaloceles mainly of those of genetic origins.

Keywords: Omphalocele, Abdominal wall defect, Genetic disorders, Congenital malformation

Background

Omphalocele, also called *exomphalos*, is a congenital malformation due to a defect in closure of the anterior abdominal wall [1–3]. This leads to midline herniation of the abdominal viscera covered by a membranous sac, into the base of the umbilical cord insertion [1, 4, 5].

It is a rare and serious condition. However, it is one of the most common anterior abdominal wall defects [6]. As the defect is observed in the Congolese fetuses or newborn babies, the purpose of this review is to clarify the main genetic risk factors associated with the omphalocele. This review is imaged by three omphalocele cases originated from Congo and France (Figs. 1 and 2). The Congolese cases: a newborn (with isolated omphalocele) (Fig. 1a) and one fetus (with trisomy 13) (Fig. 2a) have been examined respectively in the department of Surgery Paediatrics of Brazzaville's teaching hospital (TH) and in the Genetics Unit of the Health Sciences Faculty of Brazzaville. The French fetus (with trisomy 13) (Figs. 1b and 2b) has been examined in Department of Fetopathology of Pellegrin's TH (Bordeaux, France).

Main text

Embryologic origin

Embryologically, omphalocele is an embryopathy resulting from an error in a midline abdominal wall development in early embryonic development (ED). Indeed, the normal development of the primitive intestine allows at 6 weeks of ED a normal physiologic herniation of the primitive mid-gut after undergoing the 90 degrees counterclockwise rotation back into the umbilical cord [7]. The mid-gut protrudes from the abdominal cavity (which is too small to contain it) into the umbilical cord [2, 7]. In the normal state, at the age of 10 until 11 weeks of ED, the primitive mid-gut undergoes again the 180 degrees counterclockwise rotation and returns completely into the abdominal cavity from the yolk sac. The physiologic hernia disappears with complete closure of the umbilical ring [7, 8].

At the origin of the omphalocele, one incriminates two failures [8]: (i) an incomplete embryonic lateral plicature between 4 and 8 weeks of ED. The two lateral folds (right and left) of mesoderm (at the origin of the serous membrane of organism) do not close at the site of umbilical insertion. (ii) An incomplete migration and differentiation of mesodermal somites into myotomes from which originate cutaneous tissue and abdominal wall muscles [8]. This leads to an incomplete closure of umbilical ring. The mid-gut fails the rotation and do not return into the abdominal cavity. The fetal bowels and

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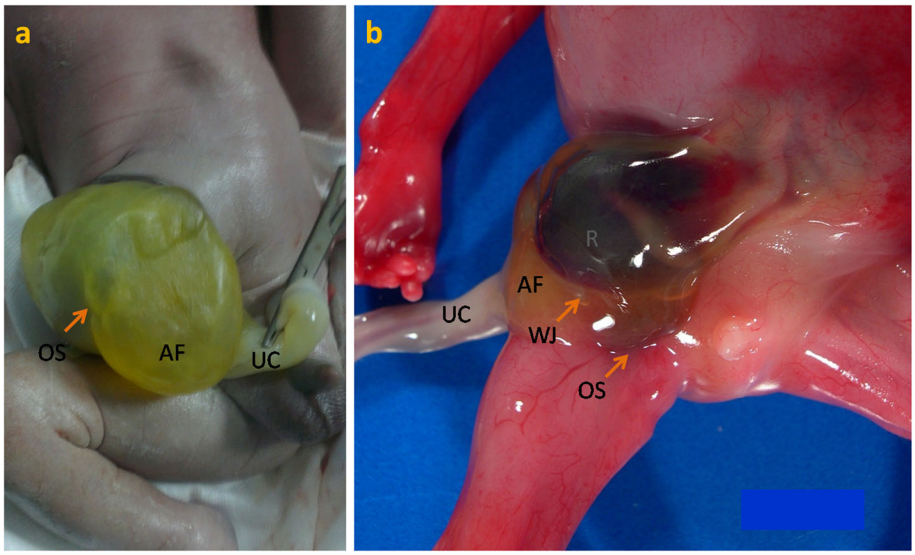

Fig. 1 Intact central omphalocele. **a** Isolated omphalocele in male liveborn Congolese infant (before surgery): medium-sized omphalocele covered with a thin sac (os) of membrane containing the amniotic fluid (AF, yellow) and the intestines. Umbilical cord (UC) inserted into the omphalocele. **b** Omphalocele in male French Fetus: medium-sized omphalocele (os) containing the spleen (R), covered with a translucent sac of fused membrane of amnion, peritoneum and the Wharton's jelly between the membranes. Umbilical cord inserted into the omphalocele

other abdominal organs protrude through the opening, giving the omphalocele (Figs. 1 and 2).

We note that the abdominal wall defects may occur in different locations during embryogenesis, showing the full complexity of the condition. In fact, there are three classes of omphaloceles based on the site of the defect and umbilical cord insertion [9]: (i) epigastric (or cranial) omphaloceles, concern the upper abdominal wall and do not reach the umbilicus. The most severe form is the pentalogy of Cantrell. (ii) Central omphaloceles, concern the middle abdominal wall and are periumbilical. They are the most common. (iii) Hypogastric (or caudal)

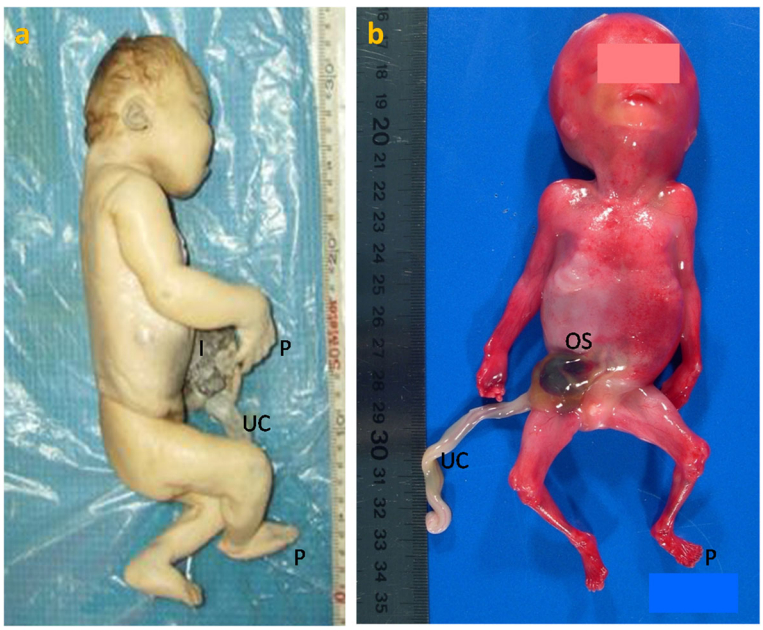

Fig. 2 Omphalocele in fetuses with trisomy 13. **a** Male Congolese fetus born dead. Ruptured omphalocele (o) with eviscerated small intestines (i) and umbilical cord (UC) inserted in the omphalocele. Dysmorphic facies with microcephaly, cleft lip, ears down inserted. Bilateral postaxial polydactyly (P) of hands and feet. **b** Male French fetus after termination of pregnancy. Intact omphalocele (o), dysmorphic facies with microcephaly, cleft palate, low set ears, postaxial hexadactyly of hands and feet

omphaloceles, concern the lower abdominal wall, under the umbilicus and are always associated with urorectal anomalies.

Epidemiology

The prevalence of omphalocele is variable according to the series and the country. The approximate prevalence is in the range of 1:4000 to 1:7000 live births [4, 9, 10]. The large American and French cohort omphaloceles have given respectively a mean prevalence rate of 1.92 and 2.18 per 10,000 live births predominant in male neonates [11, 12]. Compared with congenital malformations, in Morocco, the prevalence rate of reported omphalocele was 1% of congenital malformations for a period of 8 years [5]. In Congo, the medical records of 430 congenital malformations seen in Pediatric services of TH for a period of 5 years showed four omphalocele cases in liveborn infants, i.e., a prevalence of 0.93% of congenital malformations. The male to female sex ratio was 1:1.

Diagnosis and content

Imaging allows the identification of omphalocele from early antenatal period, by the fetal ultrasound screening (in 67.2% of cases) in the first and second trimesters (since the gestational age 12-14 weeks and later) or by resonance magnetic imaging (RMI), computed tomography scan and by abdominal X-ray in neonates [1, 4, 13–15].

The maternal serum alpha-fetoprotein and the dosage of acetylcholinesterase in the amniotic fluid are used in antenatal period for omphalocele screening. The tests can reveal an elevated level of those biomarkers [1, 5]. Genetic analysis (for etiological research) is recommended, especially karyotype and or chromosomal microarray.

The omphalocele images are characteristic (Fig. 1a, b): the hernia containing the abdominal viscera embedded in amniotic fluid is covered by a thin sac of fused membranes of amnion (externally) and peritoneum (internally), with the Wharton's jelly between the two components [1, 4, 6, 9]. The umbilical cord is abnormally inserted into the omphalocele sac [15]. The eviscerated organs are predominantly intestines (illustrated by Fig. 2a), liver or spleen and pancreas as observed in one our fetuses (Figs. 1b and 2b), rarely colon, ovaries or stomach [1, 5, 14].

Associated congenital anomalies

Omphalocele is sometimes associated with other congenital malformations which increase the newborns mortality and the defect seems to be more prevalent in male gender. The prevalence of associated anomalies is in 31 to 50% of omphaloceles or more (63 to 80%) according to the series [6, 10, 13, 16–18]. These additional anomalies are various, and all organs can be affected depending on the etiology [19]. They can be: neural tube defects (anencephaly, holoprosencephaly, spina bifida and rudimentary orbits), cleft palate, single umbilical artery, amniotic fluid anomaly (oligoamnios or polyhydramnios) [6, 20]. Other associated anomalies include cardiovascular defects (the most common up to 40%), digestive (like Meckel's diverticulum), metabolic, musculoskeletal or urogenital anomalies (for example micropenis and multicystic kidneys) [2, 4, 11, 13, 16, 21]. In regard to these associated anomalies, a fetopathological examination (for the fetuses) and a complete clinical examination of the neonate are needed.

Genetic origins

Genetic diseases and polymalformative syndromes are commonly diagnosed in fetuses and neonates with omphalocele. In the most cases (28 to 50%), omphaloceles are isolated and are considered as sporadic and weakly recurrent [22–24]. In most cases (more than 50%), the malformation is linked to various pathologies and can be a call sign of genetic disorders [9, 16]. Genetic risk factors are the commonest one: firstly chromosomal aberrations, secondly genetic syndromes, and thirdly polymalformative syndromes. In addition, several genes are related to omphalocele.

Chromosomal aberrations

They are involved in 38 to 67% of the omphaloceles, mainly the aneuploidies [2, 9, 25]. The most frequent are as follows: trisomy 18 which ranks the first place (22 to 89% of fetuses having omphalocele) and trisomy 13 which clinical features are represented by Fig. 2 (trisomy confirmed by the karyotype not shown) [9, 15, 26, 27]. The data compilation of the chromosomal anomalies from literature (Table 1) gives the average incidence of 77.2% for trisomy 18 and of 11.4% for trisomy 13, in coherence with the published data. It may be noted that chromosomal anomalies are more associated with central omphalocele [9]. Other chromosomal aberrations that can be identified are for instance: triploidy; monosomy X (Turner syndrome); 47, XXY (Klinefelter syndrome); trisomy 16 and 21 (very low contributors); partial trisomy such as dup (1q), dup (3q), dup (4q), dup (5p), dup (6q), dup (11p), dup (15q23), dup (17q) or deletion like del (1q), del (9p); inv (11) [14, 16, 29–31].

Genetic syndromes

Familial syndromal forms of omphalocele over two generations (requiring genetic counseling) are reported [23, 24, 32]. The mode of inheritance can be autosomal dominant, autosomal recessive or X-linked trait [3, 24, 32]. The most common syndrome is the Beckwith-Wiedemann syndrome (BWS), seen in 3 to 22% of omphaloceles [4, 22, 27]. BWS is a paternal uniparental disomy (UPD) of 11p15 imprinted region, inherited in autosomal

Table 1 Median incidence of common chromosomal anomalies in omphalocele

No.	% CA	Trisomy 18	Trisomy 13	Trisomy 21	Triploidy	TS	KS	Others	Authors
90	48.9 (44/90)	33	5	1	2	1	-	2	Brantberg et al., 2005 [9]
26	38 (10/26)	4	4	1	-	1	-	-	Nyberg et al., 1989 [25]
67	39 (26/67)	21	2	1	-	1	-	1	Fratelli et al., 2007 [26]
35	34 (12 /35)	10	2	0	-	-	-	-	Emer et al., 2015 [28]
35	54 (19/35)	17	-	-	1	-	1	-	Chen et al., 2007 [29]
18	67 (12/18)	10	1	-	1	-	-	-	Chen et al., 2007 [29]
271	(*n* = 123) 45.4	9577.2%	1411.4%	32.4%	43.25%	32.4%	10.8%	32.4%	

No., number of omphalocele; *CA*, chromosomal abnormalities; *n*, number of CA; *S*, syndrome; *T*, Turner; *K*, Klinefelter

recessive manner. The latter condition associates the following clinical features: polyhydramnios, macrosomia, macroglossia, visceromegaly, abdominal wall defect, external ear abnormalities and hypoglycemia (to the neonate) [4, 9, 29]. Paternal UPD of 14q32 imprinted region has been also reported. It concerns Kagami-Ogata syndrome inherited on autosomal dominant mode. The clinical signs include: a characteristic facies, small thorax, abdominal wall defects, placentomegaly and polyhydramnios (OMIM # 608149) [33]. Other genetic syndromes associated with omphalocele are for instance: Miller-Dieker lissencephaly syndrome (microcephaly, lissencephaly, small brain, deletion on 17p13.3 band inherited on autosomal dominant mode); Pallister-killian syndrome (coarse dysmorphic facies, mental retardation, skin anomalies, tetrasomy 12p); Meckel-Grumber (occipital encephalocele, postaxial polydactyly, multicystic dysplastic kidneys, inherited on autosomal recessive mode); Goltz syndrome (X-linked dominant trait) and Marshall-smith syndrome [13, 29, 30].

Polymalformative syndromes

Omphalocele may be a part of morbid polymalformative syndromes (PS), recurrent in some families. Among them are the OEIS complex (3% of omphaloceles) which is a combination of the following defects: hypogastric omphalocele, exstrophy of bladder, imperforate anus and spina bifida) [13, 22, 34]. Deletion of 1p36 has been described (OMIM # 258040). Another PS is the pentalogy of Cantrell which associates an epigastric omphalocele, a diaphragmatic hernia, an agenesis or a bifid sternum, a cardiac ectopia (or ectopia cordis) and an intra-cardiac defect [4, 5, 28, 35]. The condition can be inherited in X-linked dominant mode in the region Xq25-q26.1 (OMIM # 313850); Familial cases of Prune Belly (Eagle-Barrett syndrome) inherited in autosomal recessive manner have been reported and the chromosome regions identified were 1q41-q44 and 11p11 (OMIM # 100100). The phenotype includes: abdominal muscle deficiency, cryptorchidism and urinary tract malformation, is also associated with omphalocele [19].

Generally, omphaloceles originating from genetic origins are small (with often an intestinal content) and associated anomalies are more frequent [1, 9, 25, 30]. Their prognosis especially in presence of additional malformations or chromosomal aberrations is less good than in isolated omphaloceles [2, 9, 11, 27].

Gene mutations

Several genes (MalaCards 2019, 2013 GRCh38/hg38) are indexed in the occurrence of omphalocele, among which *CDKN1C* (cyclin dependent kinase inhibitor 1C) or *P57kip2*, an imprinted gene with maternal expression, mapped on 11p15.4 imprinted region. The gene is involved in cell cycle and acts as negative regulator of cell proliferation. *CDKN1C* mutation causes BWS associated with omphalocele [36]. *Alx4* (Aristaless-like Homeobox 4) located on 11p11.2 chromosomal band, belongs to the homeobox family. It plays an essential role in skeletal and skin development and it is high expressed in skeletal and smooth muscles. Disorder in Alx4 causes omphalocele in mice [37]. *FGFR1* and *FGFR2* (fibroblast growth factor receptors 1 and 2) are thyrosine protein kinase respectively located on 8p11.23 and 10q26.13. They play a role in the regulation of embryonic development and are expressed in ectoderm of the abdominal wall. Their conditional both mutation also results in an omphalocele in mice [38]. We have in Table 2 reported other susceptibility genes for omphalocele (MalaCards 2019; 2013 GRCh38/hg38) [31, 39, 40].

We can also mention that it exists other causes than genetics, indexed in the occurrence of omphalocele, for instance: consanguineous parents, obesity, maternal age (young or advanced), multiple gestation, water soluble vitamins and cofactors (folic acid, vitamins B complex), environmental factors, intake by the mother of antithyroid drugs, antiepileptic (valproic acid) and alcohol (Mala Cards 2019) [1, 5, 11, 41].

Differential diagnosis and treatment

The differential diagnosis of omphalocele is mainly made with the following: (i) the gastroschisis: it is a herniation of intestinal structures, right para-umbilical, not covered

Table 2 Genes related to omphalocele (MalaCards 2019; 2013 GRCh38/hg38)

Genes	Location	Activity	References
PLOD1 (Procollagen-lysine, 2-oxoglutarate 5dioxygenase1)	1p36.22	Epidermis development, stability of the intermolecular collagen cross-links. high expressed in skeletal and smooth muscle	Tosun et al., 2014 [39]
Msx1 (Msh homeobox 1)	4p16.2	Embryonic morphogenesis, multicellular organism development. Regulation of cellular proliferation and differentiation	Doi et al., 2010 [40]
Msx2 (Msh homeobox 2)	5q35.2		
NUAK1 (SNF1-like kinase, 1) Omphalocele kinase 1	12q23.3	Regulation of cell adhesion and cell proliferation. Expressed in heart, brain, skeletal and smooth muscle	2013 GRCh38/ hg38
NUAK2 (SNF1-like kinase, 2) Omphalocele kinase 2	1q32.1		
GJB2 (Gap Junction Beta-2 Protein)	13q12.11	Connexin family. Cell communication expressed in the suprabasal layer of the epidermis.	Zhou et al., 2018 [31]
GLCE (D-glucuronyl C5-epimerase)	15q23	Highly expressed in the digestive tract and the skin	Zhou et al., 2018 [31]
RPLP1 (ribosomal protein lateral stalk subunit P1)	15q23	Structural constituent of ribosome, activator of protein kinase activity	Zhou et al., 2018 [31]

by a membranous sac, and the umbilical cord is normally inserted in the abdominal wall [1, 3]; (ii) umbilical hernia: consists in a slippage of the digestive tract in the umbilical cord and it is skin covered [3, 5]. (iii) The persistence of the physiological gut herniation: it is small (inferior to 7 mm of diameter) and exceeds 12 weeks of ED [5].

Concerning the treatment, the condition is a medical and surgical emergency when the newborn is alive and is depending on the size of the defect. Two types of surgical closures are proposed: primary closure (just after birth) for small-sized omphaloceles and delayed closure (later) for giant omphaloceles [2, 6, 10].

The prognosis

The associated congenital anomalies, the ruptured sac and the size of omphalocele determine the prognosis of the newborn. Omphaloceles are classified as small or giant defect and there are many anatomic classifications that determine the prognosis. The most used is Aitken classification (Table 3), and the type I (small-sized defects, inferior to 4 cm) have excellent results with the survival rates of 90 to 97%, if they are isolated [5, 6, 9, 21]. Ndour et al. [19] reported in their series an overall mortality rate of 45.3% (less prevalent in isolated defects). In one Nigerian study, omphalocele accounted for 18.3% of the neonatal surgical pathology and the rate post-operative mortality was of 26%, while it was of 15% in one Moroccan published study [5, 42]. A new insight for the type II giant omphaloceles (defects greater than 5 cm or presence of liver) is the possible conservative management at birth with delayed surgical closure of the ventral hernia after [10]. Topical agents are used before, to promote escharification and epithelialization of the omphalocele sac [10, 21]. The therapeutic approach seems to be controversial (it can reduce the mortality rates in some cases and can increase mortality rates in other cases.

Table 3 Omphalocele Aitken classification

Type	Criteria
I	Larger of defect (collar base) < 4 cm
	Diameter of the sac < 8 cm
	Absence of liver
II	Collar base > 5 cm
	Diameter of the sac > 8 cm
	Presence of the liver in the sac

Type I: all criteria must be present
Type II: presence of one criterion is sufficient

Conclusion

This paper mainly based on a review, shows than genetic disorders; predominantly chromosomal aberrations (aneuploidies) are providers of omphalocele. So fetal or neonate karyotyping is recommended in the latter. The additional congenital anomalies, familial omphalocele history, and advanced maternal age (indexed in the occurrence of aneuploidy) may alert the clinicians in the search of a genetic disease which can necessitate genetic counseling in inherited and recurrent cases.

Abbreviations

AF: Amniotic fluid; BWS: Beckwith-Wiedemann syndrome; del: Deletion; dup: Duplication; ED: Embryonic development; i: Intestines; OEIS: Omphalocele, exstrophy, imperforate, spina bifida; OS: Omphalocele sac; P: Polydactyly; PS: Polymalformative syndrome; RMI: Resonance magnetic imaging; TH: Teaching hospital; UC: Umbilical cord; UPD: Uniparental disomy

Acknowledgements

We would like to thank the patient families and clinicians who provided the photos.

Authors' contributions

All authors have contributed to write this paper. They have read and approved the final manuscript.

Funding
Not applicable.

Availability of data and materials
Not applicable

Ethics approval and consent to participate
Not applicable

Consent for publication
Obtained.

Competing interests
The authors declare that they have no competing interests.

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Received: 9 August 2019 Accepted: 5 November 2019
Published online: 27 December 2019

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