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MAIN TOPIC

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The pathogenesis of omphalocele and gastroschisis

An unsolved problem

Abstract The embryology of gastroschisis and omphalocele remains a matter of speculation. Most authors still assume that they represent seperate entities with a different pathology and embryology. In contrast, others feel that gastrochisis is simply the end-result of a ruptured omphalocele. Reviewing the current literature on the normal and abnormal embryology of the anterior abdominal wall, it becomes obvious that appropriate embryological knowledge of these processes is still missing. Animal models are not at hand that would allow clear definitions of morphological changes unique to either malformation. Nevertheless, our own observations of the pathological anatomy of these anomalies lead us to believe that the abdominal wall defects are the result of disturbed development of the embryonic umbilicus. This includes gastroschisis, which is more likely a ruptured small omphalocele than a developmental entity of its own. In our view, the common ventral abdominal wall defects fall into two main categories: (1) large omphaloceles; and (2) small omphaloceles, with gastroschisis as a subentity of this lesion.

Key words Anterior abdominal wall, normal and abnormal development · Omphalocele · Gastroschisis · Pathological anatomy

Introduction

In the pediatric surgical literature, the true nature of gastroschisis (GS) and omphalocele (OC) is still under debate. While some pediatric surgeons and embryologists believe that they represent separate entities with different pathology and embryology [3, 10, 14], others maintain that GS is the end-result of a ruptured small OC, and they therefore represent rather similar abnormalities [9, 17, 19].

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The reasons for this debate include the similarities on the one hand and the differences in the pathology and clinical presentation on the other, as well as the lack of appropriate embryological knowledge of the normal and abnormal development of the ventral abdominal wall. Animal models are not available that would allow clear definitions of morphological changes unique to either malformation.

Pathology and clinical presentation

Until 1953, the term "GS" was used for all types of upper abdominal wall defects with the exception of the physiologic hernia of the umbilical cord [12]. In this year, Moore and Stokes [15] redefined the term "GS" and restricted it to ventral abdominal wall defects without a sac. In contrast, those defects with a sac were referred to as "OC". "Exomphalos" and "amniocele" are synonymous with OC and are used to describe identical pathological findings.

Pathology of omphalocele

Omphalocele is defined as an "anterior midline defect of the abdominal wall through which various viscera herniate into an avascular hernial sac" [12]. Benson et al. [4] subdivided these defects according to their size and extent. They used the term OC for anterior abdominal wall defects larger than 4 cm and extending into the supraumbilical region and termed all smaller defects with herniation through the umbilical ring only "hernia of the cord".

Bax et al. [2] used the presence or absence of liver in the sac to distinguish between large and small OCs. Nakayama et al. [16] used the same criterion for prenatal assessment of fetuses with abdominal wall defects.

In small OCs ("hernia of the cord") the umbilical cord usually emerges from the tip of the sac, while in large OCs it emerges from the caudal part of the sac or sometimes even from the caudal border of the defect [3, 12].

Pathology of gastroschisis

Gastroschisis was initially defined as a "defect of the abdominal wall in an extraumbilical location and without a membranous sac" [17]. In the vast majority of cases, the defect seems to be located to the right of the midline and to the right of a normally positioned umbilicus [10, 14, 15, 20]. In single reports, left-sided defects were reported by deVries [7] and Toth and Kimura [21]. According to Irving [12], GS is a full-thickness defect of the abdominal wall that is in close approximation to the umbilical cord and is sometimes separated from the cord by a bridge of skin [12, 14, 15]. Through this defect, the stomach, intestine, and parts of the colon may herniate while the liver remains in nearly all cases inside the abdominal cavity [2].

In general, GS is defined by the following pathological findings [17, 19]: (1) a "normal" umbilical cord located almost always to the left of a "full-thickness" [12] defect, occasionally separated from it by a bridge of skin; (2) absence of a sac; (3) matting and thickening of the eviscerated bowel with a "peel"; (4) extreme rarity of herniation of significant portions of the liver; (5) frequent infarction or atresia of the herniated bowel; and (6) infrequent association of malformations of other major organ systems.

Embryology of ventral abdominal wall defects

In 1990 Irving stated that "there is still considerable controversy about the precise embryogenesis of exomphalos (omphalocele) and gastroschisis, the main point at issue being the question whether the two lesions represent distinct developmental anomalies or whether they have a common embryogenesis" [12]. The main reason for this controversy is the lack of an appropriate animal model for GS and OC that would allow a precise definition of all embryological steps that finally lead to the different types of abdominal wall defects.

In normal human embryos, there are no embryological stages resembling the pathological pictures of OC and GS. The exception is the "hernia of the cord", which is similar to the "physiological hernia" in human embryos between the 5th and 10th week of gestation. However, the liver is never involved in such a physiological hernia, and therefore, the embryological explanation of large OCs with liver in the sac is not that simple.

Obviously, an OC is the result of a primary malformation of the ventral wall of the embryo. However, the mechanisms involved are still obscure. Many authors presume that the normal closure of the ventral abdominal wall of the embryo is impaired [7, 10], but the exact process of maldevelopment is still unknown.

Normal embryology of the ventral abdominal wall

The development of the ventral body wall is the result of an extreme imbalance of growth of the various embryonic parts. Young embryos 2 weeks of age are in the form of a disk with two epithelial layers: ectodermal epithelium dorsally and entodermal epithelium ventrally. The ventral epithelium of the gut is continuous with the yolk-sac, while the dorsal epithelium is continuous with the amnion. Extensive growth of the embryo along its long axis leads to the formation of head and tail. Furthermore, the amnion expands. As a result, the borderlines between the entoderm and yolk-sac and between ectoderm and amnion are pushed toward the ventral side of the embryo, forming two sets of folds: (1) the entodermal folds of the anterior and posterior intestinal ports; and (2) the ectodermal head and tail-fold. The latter incorporates the so-called body stalk, which contains the allantois.

At the same time, the intraembryonic coelom is formed by fusion of numerous vesicles in the mesodermal parts of the embryonic head region. This splits up the formerly "solid" body of mesoderm and finally leads to the formation of the pericardium and the pericardopleuroperitoneal canals, which are the forerunners of the thoracic cavity. The mesoderm layer that is in direct contact with the coelomic cavity is transformed into an epithelial layer, which is called "splanchnopleura" when it covers entodermal organs (lung bud, gut) and "somatopleura" when it serves as the inner layer of the body wall. In some places, the somatopleura may be in direct contact with the embryonic ectoderm. In others, undifferentiated mesenchymal cells may intervene between these layers. In the region of the pericardium, the splanchnopleura is further specialized and forms the myoepicardium of the heart.

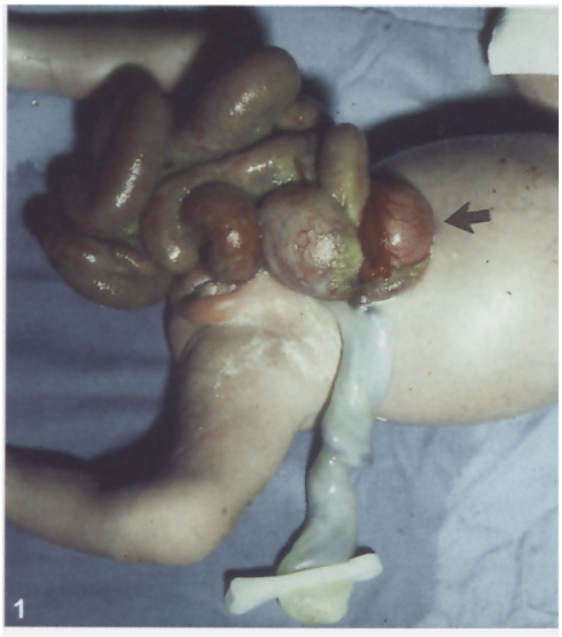
The embryonic umbilicus

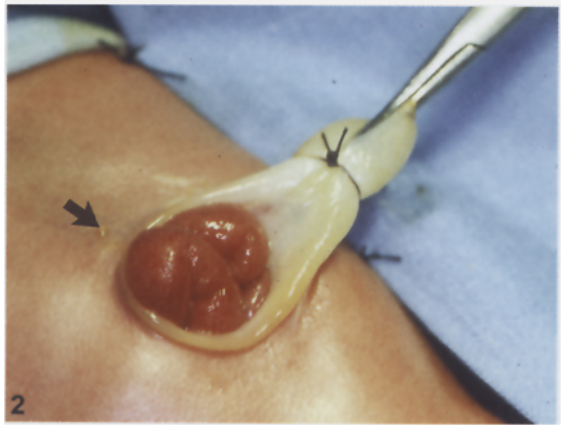
The umbilicus is by no means a uniform structure: the cranial and caudal parts are quite different. While the caudal part contains the massive body-stalk, and is therefore "fixed", the cranial part and lateral borders are formed by the epithelium of the amnion and by somatopleura. The "free" cranial border of the umbilicus is pushed caudally, first by the developing heart and later by the growth of the liver. This explains the caudal position of the umbilicus during the whole embryonic period.

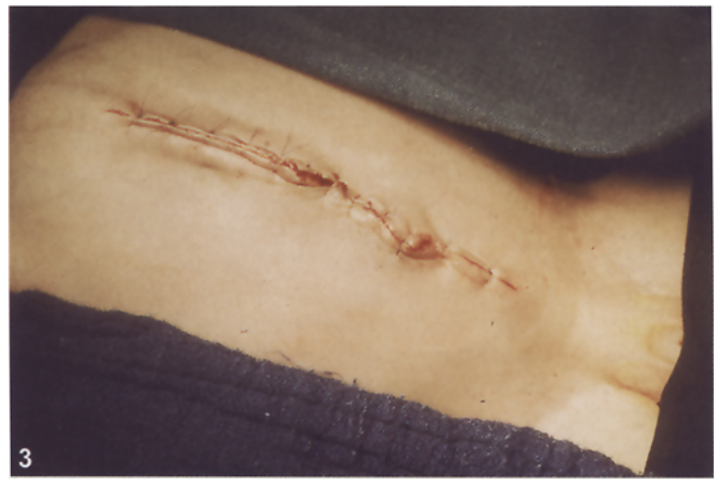
Abnormal development of the anterior body wall

In the literature, numerous theories have been proposed to explain the embryological background of OC and GS. Until 1953, true forms of GS were seldom observed [17]; therefore, most authors prior to this date only tried to explain the existence of OCs. Gross and Blodgett [11] thought that OCs were caused by a developmental arrest of the body cavity, which would stop expanding between the 8th and 12th week of pregnancy. As a result, the midgut cannot return into the abdominal cavity around the 10th week and thus remains in an abnormal position inside the umbilical cord.

According to Margulies [13], the structural defect of the abdominal wall that finally results in the formation of the







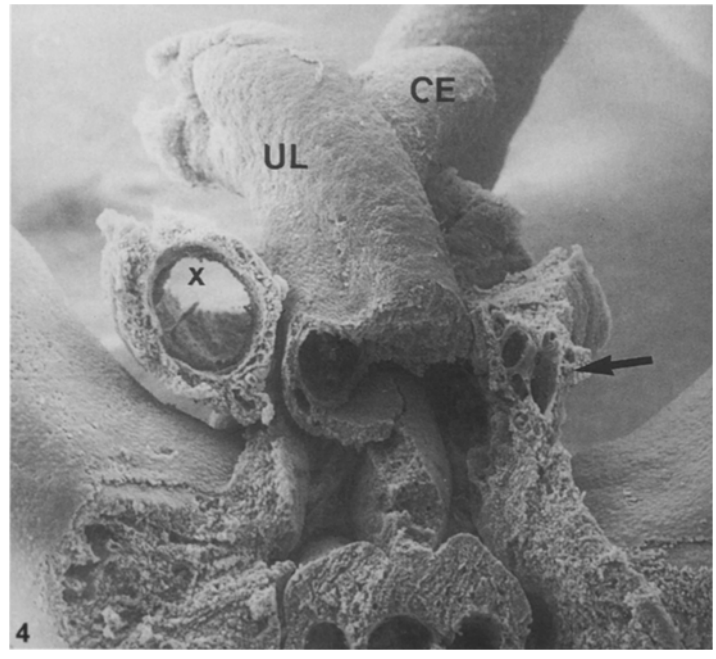


Fig. 1 Newborn with gastroschisis, large defect. *Arrow* points to linea alba. Defect is central, umbilical cord to left of midline

Fig. 2 Small abdominal wall defect (gastroschisis). Defect is central, gut already pushed back into abdominal cavity. *Arrow* marks linea alba

Fig. 3 Scar after primary closure of gastroschisis (14 days after surgery). Suture line runs exactly in midline

Fig. 4 Scanning electron microscope (SEM) picture of 14-day-old rat embryo, cranial view. Left umbilical vein is marked by *x*, right umbilical vein is in regression (*arrow*). At this stage, gut loop (UL) has already reached its position inside umbilical cord (*CE*, cecum)

OC occurs before the end of the 3rd week of embryonic development; he believed that in normal development the formation of the abdominal wall is complete by this time. Gray and Skandalakis [10] believe that OC is the result of developmental arrest at the time of the physiologic herniation of the gut into the coelomic cavity of the umbilicus. Later, the return of the gut into the abdomen either fails or is complete. Both authors believe that other organs, such as the liver, may herniate secondarily through the umbilical ring.

Irving [12] proposes that the pathogenesis of small OCs is different from that of large ones. In her opinion, hernias of the cord simply occur when the return of the gut into the abdominal cavity remains incomplete, with secondary failure of closure of the umbilical ring. She believes that delayed involution of the omphalomesenteric duct may be a causative factor, because an adherent Meckel's diverticulum seems to be a frequent finding in small omphaloceles [12]. In her view, the pathogenesis of large OCs is not that simple: in these cases a primary malformation of the ventral wall of the embryo seems to result from a disturbance in the mechanisms of closure of the embryonic body wall. She cites deVries [2], who stated that in an embryo of 24 mm crown-rump length the paraumbilical area was histologically still indistinguishable from the tissue of the umbilical cord. He concluded that an arrest of abdominal wall development at this stage (or earlier) would result in a large or moderate-sized omphalocele [7], which would be centrally located.

While some authors believe that GS is simply a ruptured small OC, others insist that GS is a distinct anomaly with a separate embryological etiology than OC. In 1963, Duhamel [8] described GS as a localized event of teratogenetic impairment of somatopleural mesenchymal differentiation with subsequent reabsorption of the overlying ectoblastic layers. Conversely, OC should originate from a primary "failure of formation of the lateral fold."

Gray and Skandalakis wrote in the first edition of their book *Embryology for Surgeons* [10]: "The defect lies in the failure of the musculature migrating from the dorsal myotomes completely to invade the splanchnopleure of the embryonic abdominal wall." In the second edition [20], the authors admitted that an adequate embryological explanation of GS does not exist. In contrast to this statement, deVries [7] believes that GS can be explained embryologically, and suggests that the disruption of the somatopleure close to the base of the stalk is due to a disturbed pattern of circulation in this area. This disturbance may occur when the involution of the right umbilical vein is "abnormal in either duration or extent" [7]. The abnormal involution may cause a localized infarction of the somatopleure, with subsequent failure of skin formation in the same area.

Discussion

Many clinicians, as well as embryologists, believe that congenital malformations are best explained by a process of inhibition of normal embryonic development [18]. Thus, most workers in this field believe that the normal process of ventral abdominal wall closure can be hampered at any stage, resulting in the widely known spectrum of OC. On the other hand, it is reversely assumed that the observed malformation represents a "frozen" stage of normal embryology [18]. However, until now embryos with the typical presentation of a large OC as a normal stage of development have not been published. Therefore, all theories expounded to explain both normal and abnormal stages of ventral wall development are not the result of embryological observations, but rather are interesting interpretations of pathological anatomic findings.

Between the 5th and 10th week of development, a part of the midgut grows and develops outside the embryo in the coelomic cavity of the umbilicus. This normal developmental process is often referred to as the physiological herniation of the gut. However, liver, stomach, and spleen never herniate into the extraembryonic coelom of the umbilicus in normal development. It is therefore impossible to explain large OCs on the basis of a "failed return of the gut" after a physiological herniation as has been done by Gray and Skandalakis [10].

Usually, large OCs with liver inside the sac present with an epigastric extension of the defect. In these cases, a combination with anomalies of the heart and other organs is quite frequent [5]. Small OCs are more centrally located; they rarely contain liver, and the combination with anomalies of other organs is rare. It is therefore likely that the site of the defect is of major importance for the clinical presentation. DeVries defined OC as a "persistence of body stalk tissue in the area normally occupied by differentiated abdominal wall" [7]. However, this description does not explain which mechanisms are in play. Furthermore, in large OCs not only the abdominal wall is abnormal, but a part or all of the liver is in an abnormal position. This could be due to faulty development of the umbilical ring, which would allow the liver to develop in an abnormal position. On the other hand, abnormal and extensive growth of the liver in a ventral direction may block the normal downgrowth of the cranial umbilical border. Both mechanisms would result in abnormal extension of the umbilicus into the epigastric region.

In contrast to these complex defects, small OCs (hernias of the cord) are probably the result of a simple developmental arrest of normal closure of the umbilicus. In these cases, the opening between the extraembryonic coelom of the umbilical cord and the abdominal cavity is centrally located, without a cranial or caudal shift. In our opinion, "hernias of the cord" are quite different from large OCs in both their clinical presentation and their embryological background. Therefore, we are in agreement with Bax et al. [2] and Nakayama et al. [16], who defined a borderline between "large" and "small" defects based not only on size, but also on the presence or absence of liver inside the sac of the OC. We have to admit, however, that precise data on the embryological background will not become available without an appropriate animal model.

It remains questionable whether a reasonable embryological explanation for GS will ever be achieved. There is much evidence that GS is more likely the end-result of a ruptured small omphalocele than a malformation on its own [6, 17, 19]. If this assumption is true, certain pathological findings must be present in the newborn with this lesion. In GS, the defect must be located centrally, since a hernia of the cord is located centrally. The umbilical cord must be attached to that side of the defect where the umbilical vein is connected to the body wall. Usually this is on the left, however, in those rare cases with a right-sided umbilical vein, the umbilical cord must be positioned to the right of the defect.

Pathologic-anatomic data strongly support these assumptions. It is well known that the defect in GS is localized between the two rectus muscles [10]. This finding is in contradiction to all theories that explain GS as a result of a right-sided lateral body wall defect [8]. We recently reviewed our cases of GS and found several forms that fit into the criteria suggested above. In Fig. 1, the rather large defect is centrally located. The umbilical cord, which is actually part of the defect, is clearly positioned to the left of the midline. In Fig. 2, the same pathology is demonstrated. This defect is rather small; again, the umbilical cord lies to the left of the midline and the defect is in a central position. After surgical correction of the defect, the suture line of the skin always runs straight in the midline of the anterior body wall, which is only possible when the initial defect was located centrally (Fig. 3).

Other observations are also in favor of the theory that GS is actually a ruptured OC. Shaw [19] published the picture of an 8-week embryo with a ruptured OC. Glick et al. [9] described the rupture of an OC between the 27th and 34th weeks of gestation. In 1980, deVries made an attempt to explain GS embryologically [7]. He assumed that a defect at the borderline between body wall and body stalk (umbilical ring) could result when the involution of the right umbilical vein is either too fast or prolonged. He speculated that at the time of physiological herniation the gut would not be pushed through the normal opening of the umbilical ring, but rather through the opening of the defect.

We feel that clear evidence supporting this assumption is missing. In normal rat embryos the involution of the right umbilical vein takes place at the 14th and 15th gestational days (Fig. 4). However, at the same time the tip of the midgut loop is already in the extraembryonic coelom of the umbilicus. It is therefore unlikely that this stage could serve as a starting point for this malformation. These data indicate that an adequate embryological explanation of GS is still missing. Clinical observations in the literature [9, 17, 19] and our own data support the idea that GS represents the end-result of an intrauterine rupture of a small OC, which means that the common ventral abdominal wall defects fall into two main categories: (1) large OCs, and (2) small OCs, with GS as a subentity of this lesion.

This classification fits well in the decision algorithm published by Nakayama et al. [16] from San Francisco.

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