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Gastroschisis: Understanding its Etiopathogenesis

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ABSTRACT

Gastroschisis has been defined as a malformation of the abdominal wall that classically presents as a visceral herniation with the presence of an intact umbilical cord and absence of a membrane covering the abdominal content. Its exact etiology is unknown; however, it is recognized that it presents a multifactorial inheritance pattern. Recently, an increase in the number of cases has been observed worldwide, particularly in Mexico, which is why some authors propose that
It is a silent pandemic that has not been monitored. The understanding of the etiological factors of this pathology can help to understand a little more the factors to which we are predisposed in our environment.

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INTRODUCTION

Gastroschisis is a congenital anomaly of the development of the ventral body wall, first described in 1733 characterized by the presence of a hole less than 2 cm in diameter in the abdominal wall, which allows evisceration of the intestinal loops and sometimes from the colon and other organs. Because it is not surrounded by amnion, the intestine is directly exposed to the amniotic fluid, with consequent swelling and possible damage to the seromuscular layer. Evisceration also explains the high maternal serum levels of α-fetoprotein, even higher than in the case of omphalocele . Depending on the extent of the defect, surgical reduction can be performed immediately after birth in order to avoid thermal and evaporative loss. through the exposed organs or gradually until complete closure, a modality that has shown an overall survival rate of more than 90%. [1,2]

Gastroschisis occurs predominantly to the right of the umbilical cord insertion .Rarely, it may be located on the left side but always, in contrast to the midline location of other ventral body wall abnormalities, such as omphalocele, ectopy of the heart, exstrophy of the bladder and cloaca, pentalogy Cantrell and extremity-body wall complex. Other malformations can occur simultaneously with gastroschisis - in 10-20% of cases- especially in the gastrointestinal tract, such as malrotation, volvulus, stenosis and atresia. Rarer still are other types of comorbidities, such as defects of the neural tube or diaphragm, ectopia cordis or congenital heart disease. In order to explain why the prevalence of the malformation has shown an increasing global trend in recent decades, Especially in young mothers and/or with a history of alcohol and tobacco consumption during pregnancy, multiple studies have been carried out that suggest the participation of various environmental and genetic predisposition factors as an important cause of risk. However, and despite the diversity of factors involved, to date there is no conclusive evidence about the cause of the malformation. [3,4,5]

ORIGIN OF GASTROSCHISIS: ANATOMICAL EVENTS

Until the last decade it was stated that gastroschisis was an independent malformation of the umbilical cord and that it shared with the other congenital anomalies of the ventral body wall, except for omphalocele, a common embryonic mechanism associated with defective fusion of lateral body folds, as a cause of abnormal closure of the thoracic and abdominopelvic cavities. For omphalocele, a failure in the return of the intestinal loops from the umbilical coelom to the abdominal cavity was proposed, after the physiological herniation that normally must occur between the sixth and twelfth week of development. In agreement with these

premises, as a result of a teratogenic exposure during the fourth week, the affected somatopleura did not develop normally, so that an orifice devoid of ectoderm appeared in the abdominal wall, through which the intestine protruded. [6,7,8]

At that time no implicated teratogen was proposed, nor was it explained why it exclusively affected an area as small as the orifice. Later, a common mechanism was proposed to explain the origin of gastroschisis and omphalocele. It was proposed that, although both entities appeared as a consequence of physiological umbilical herniation, in the case of gastroschisis rupture of the amnion occurred and, therefore, exposure to amniotic fluid, also noting that in gastroschisis the rectus abdominis muscles are in normal position, on each side of the central location of the defect. Vascular alterations have also been postulated as the cause of gastroschisis. [9,10]

De Vries et al suggested that the defect could be caused by weakness and consequent rupture of the somatopleura, due in turn to the abnormal involution of the right umbilical vein, while, for Hoyme et al, the defect and the subsequent intestinal herniation they were due to the rupture of the right vitelline artery in the umbilical region, which would produce infarction and necrosis at the base of the cord. Considering that the umbilical vein does not drain the mesoderm of the umbilical region and that it is the dorsolateral aortic branches and not the vitelline arteries that supply the abdominal wall, both theories were ruled out. [11,12]

However, Lubinsky proposed a dual vascular and thrombotic model, in which the normal involution of the right umbilical vein leaves a space to the right of the umbilical ring, which is susceptible to a thrombotic event when estrogen levels are high, as occurs in very young mothers. In this case, the thrombus could damage the cellular growth of the adjacent tissue and allow herniation of the abdominal viscera. [13,14]

ETIOLOGY

In the last decade, a plethora of reports have been published on the role of genetic and non-genetic factors in the genesis of gastroschisis. Although there is no absolute certainty about the genetic origin of the malformation, there is information about familial cases of twins and distant relatives. Through a systematic review of population studies, Salinas-Torres et al found associated chromosomal anomalies and defects, with a frequency of isolated occurrence of 82.1%. [15]

The prevalence of concurrent anomalies was 17.9% and of these, the most frequent were cardiovascular and digestive. In relation to chromosomal abnormalities (trisomies 13, 18 and 21), the prevalence was greater than 3%. In the chromosomes involved, they postulated some regions significantly associated with critical biological processes for the pathogenesis of the malformation, such as vascular alterations, thrombosis and mesodermal deficiency. On chromosome 13, they identified regions 13q12.3 (FLT1), 13q22.1 (KLF5), 13q22.3 (EDNRB) and 13q34 (COL4A1, COL4A2, F7, F10), involved in blood pressure regulation, angiogenesis and coagulation; on chromosome 18, the 18q21.33 (SERPINB), 18q22.1 (CDH7, CDH19) (KRTAP (21q22.11 and 21q22.3) regions, involved with the regulation of endopeptidase activity and calcium-dependent intercellular interactions and 21q22.11 and 21q22.3 (KRTAP) regions, related to keratinization processes, on chromosome 21. [15]

Figure 1. Gastroschisis clasical presentation.

By means of bioinformatic tools and from genes cosegregated with gastroschisis, it has also been possible to recognize pathogenetic pathways involved in the closure of the ventral abdominal wall, suggesting that the anomaly could result from the interaction between biological and molecular mechanisms and genetic predisposition, during the first ten weeks of development. In this same line of reasoning, Feldkamp et al, through analysis of shared genomic segment, identified heritable chromosomal segments in high-risk multigenerational pedigrees, thus supporting the concept of the existence of genetic susceptibility. [15]

INFECTIOUS AGENTS

Feldkamp et al. reported that, among the pathogenic agents that cause sexually transmitted infections, Chlamydia tracomatis was the most frequent in the mothers of the group of cases they studied, which they explained as the result of the special affinity of the pathogen by columnar epithelial cells of cervical ectropion in adolescent women, pregnant women, and those taking estrogen-containing contraceptives. It is worth noting that these columnar cells become squamous with increasing age, which decreases the pathogen-cell affinity, as well as the probability of infection. [16]

The results of Feldkamp et al differ from those previously published by Parker et al for the first trimester of pregnancy, in that the latter found no association between reactivity in terms of IgG against the pathogen or against the chlamydial heat shock protein CHP60, which should reflect the chronicity of the infection with Chlamydia tracomatis. [16]

STRESS AS AN ETIOLOGICAL FACTOR

In addition to genetic and chromosomal alterations, and infectious agents, other factors have been involved in the pathogenesis of the malformation. Apparently, there is an association with exposure to herbicides) or pesticide with radiation, with the use of medications such as opioids, antihyperthyroids or antiasthmatics, with nutritional factors such as high caloric intake preconception with methionine and threonine deficiency or poor intake of folic acid and even with adverse maternal psychosocial conditions. [18]

As a consequence of the great diversity of risk factors that have been implicated in the aetiology of gastroschisis, the idea of a possible existence of a shared pathogenic pathway, whose activation could induce oxidative damage in response to the stress generated by said factors, is better supported. factors. It has been shown that oxidative imbalance resulting from excessive production of reactive oxygen species or from a weak antioxidant system can negatively affect early embryonic development, since newly formed and actively proliferating cells are especially vulnerable to deleterious effects. of these species on DNA, which can cause not only congenital abnormalities, but also early abortion, preeclampsia and intrauterine growth restriction. [18]

CONCLUSIONS

The information obtained in humans and in animal models suggests that it is in the defective closure of the umbilical ring and the rupture of the amnion that the origin of gastroschisis should be sought, and that these two events could occur as a consequence of oxidative damage. resulting from the activation of a common pathogenic pathway in which more than one factor with potential stress induction converges and, eventually, simultaneously with some type of genetic predisposition in the affected embryos. It is therefore feasible that the deepening of the biochemical and immunological aspects of this stress-inducing pathogenic pathway, as well as the search for genes and regulatory proteins, may in the near future contribute to dispelling the uncertainty about the etiology of the malformation, especially in cases of familial recurrences. It is also worthwhile that the decrease in the global prevalence rate of the malformation that has been reported in some countries be the subject of further study, in order to establish whether there are population factors involved.

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