PEDIATRIC THEME

New embryological hypothesis, genetics and epidemiology of gastroschisis

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ABSTRACT

Gastroschisis is defined as an abdominal wall malformation characterized by visceral herniation with an intact umbilical cord and absence of membrane. At present, six theories to explain the embryogenesis of this entity have been proposed. Although its etiology remains unknown, it is recognized with a multifactorial inheritance pattern. Recently, an increase of cases worldwide has been observed, particularly in Mexico. For that reason, some authors suggest this entity is pandemic. We performed an updated review of the abdominal wall embryology, theories, epidemiology and genetic-environmental risk factors involved in the development of gastroschisis.
Key words: gastroschisis, theories, genetic-environmental factors.

INTRODUCTION

Gastroschisis is a congenital malformation characterized by visceral herniation through a defect in the abdominal wall, usually on the right side, with the presence of intact umbilical cord and not covered by the membrane.[1] The word "gastroschisis" is derived from the Greek prefix "gaster" = stomach and "schisis" = fissure.[2] Although this term is not entirely appropriate because it does not represent all the features of this entity, its use has been accepted. Since 1056 there are Babylonian records of this malformation, but it was Lycosthenes in 1557 who first described it in the medical literature and Moore and Stokes in 1953 who classified it based on its appearance.[3]

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The prevalence of gastroschisis is 0.5-7/10,000 newborns (NB), with an average of 1/2700 births. The frequency of this malformation is higher in Mexico, lower in Slovakia and more frequent in the southern cone countries.[4] Gastroschisis is presented in isolation or associated with other malformations with a male/female ratio of 1/1.3 in isolated cases and 4/1 in nonisolated cases.[5] Since 1980 there has been an increase in frequency of 10-20 times worldwide, but the specific cause of the increase is unknown.[6,7] This malformation occurs mainly in children of young mothers (<20 years of age).[8] In Mexico, the Registry and Epidemiological Surveillance of External Congenital Malformations (RVEMCE) reported in the International Clearinghouse for Birth Defects Surveillance and Research a prevalence of 0.77 from 1982 to 1986, 1.45 from 1987 to 1991, 2.09 from 1992 to 1996, 3.75 from 1997 to 2001 and 5.34 from 2002 to 2006 (Figure 1).[9] At present it is the fourth leading cause of mortality in children <5 years, only after congenital heart malformations, neural tube closure defects (NTCD) and Down syndrome.[10]

Embryology of the Abdominal Wall

At ~21 days of gestation, the embryo is a trilaminar disk located between the amniotic cavity and yolk sac. When forming the neural tube, the disc edges are folded to form ventral folds that extend downward. Subsequently, after 24 days, the cephalic and caudal folds are formed, and

the folding of the embryo begins to give rise to the yolk stalk and body. After 28 days, the opening around these stems forms the umbilical ring, which contains the duct and vitelline arteries (yolk stalk), the allantois, the stem connector and a communicating channel between the intra- and extra-embryonic cavities. At 29 days, the intestinal tube forms a loop on which the superior mesenteric artery is formed by the coalescence of the vitelline arteries. At 37 days, the vitelline duct and the stem connector unite to form the umbilical cord. The forces responsible for this union involve the movement and fusion of the outer side toward the midline. Different mechanisms are involved in the merging process such as apoptosis, cell-cell interaction and cellular migration.[11]

Gastroschisis Development Theories

Over the years various authors proposed different hypotheses for the development of gastroschisis:

1) Duhamel, in 1963, suggested that the failure in the differentiation of embryonic mesenchyme (somatopleuric) causes growth defects of the lateral abdominal wall and herniation of the intestine due to teratogenic exposure during the fourth week of development. However, the type of teratogen is unclear and how this affects such a small area.[12]
2) Shaw, in 1975, suggested that gastroschisis is caused by rupture of the amniotic membrane at the base of the umbilical cord during the time of physiological herniation or by the delayed umbilical ring closure. This theory does not explain how the rupture occurs and how normal skin exists between the umbilical cord and abdominal wall defect.[13]
3) De Vries, in 1980, suggested that abnormal involution of the right umbilical vein leads to adverse effects on the adjacent mesoderm, followed by the subsequent rupture of the body wall. However, the umbilical vein does not drain the mesoderm of the umbilical region and veins do not degenerate until the second and third month of development, after the closure of the body wall has already taken place, making this an unlikely theory.[14]
4) Hoyme et al., in 1981, formulated the theory that the disruption of the right vitelline artery (omphalomesenteric) in the umbilical region causes infarction and necrosis of the base of the umbilical cord, rupture of the body wall and intestinal herniation through the defect. This hypothesis is no longer accepted because it has recently been clarified that the vitelline arteries supply both the intestine and the yolk sac, but not the abdominal wall, as this area is irrigated by the dorsolateral branches of the aorta.[15]

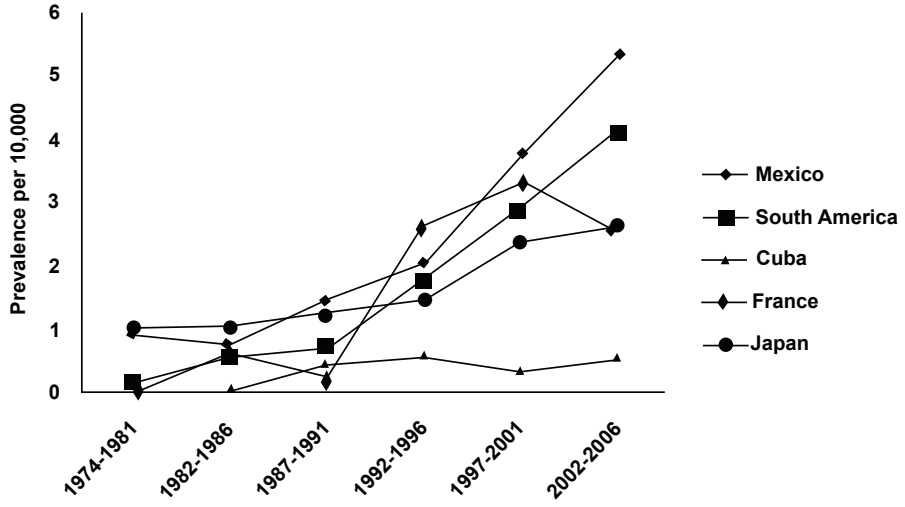

Figure 1. Graph demonstrating prevalence of gastroschisis in five geographical regions during different periods (1974-2006). There is a tendency in the increase of cases particularly in Mexico, followed by countries in South America.

5) Feldkamp et al., in 2007, argued that the abnormalities in the body fold are responsible for the body wall defects. However, most of these cases occur in the midline and not on the right side (as occurs in gastroschisis), probably due to asymmetry in body folds, position of organs and vascular development. The portion of skin between the defect and the umbilical cord may be the result of the growth of ectodermal tissues. It is important to note that this hypothesis was based on previous studies in mice where the malformation tends to be massive and lethal and would generate a defect of the limb body wall in humans.[16]

All of the previously mentioned theories have been refuted. Recently, Stevenson et al. proposed that gastroschisis is caused by the failure of the sac and yolk duct, as well as of the vitelline vessels, to initially incorporate to the allantois and later to the body stem. It has been determined that there is a second perforation in the abdominal wall, as well as that of the umbilical ring, through which the midpoint of the intestine (Meckel point) is connected to the externalized vitelline structures. These are attached to the bowel abnormally, separating it from the body stem, which causes a failure in the incorporation of the umbilical stalk. As a result, the gut is extruded into the amniotic cavity without remnants of yolk sac or amnion so that the midpoint of the intestine is always externalized and there is an absence of vitelline remnants in the umbilical cord.[17] The location on the right of the defect can be explained by the tendency of the yolk stalk to move to this side due to the presence of the heart and more rapid growth of the left lateral wall.[17,18]

Clinical Features

Gastroschisis is a paramedian defect commonly located to the right of the umbilical cord, although in rare occasions it can present itself on the left side with visceral protrusion that can be of distal ileum, stomach (48%), liver (23%) or other organs (31%).[1,19-22] The umbilical cord is found to be intact and lateral to the defect with a normal skin bridge. The size usually ranges from 2-8 cm (rarely is it a small defect <2 cm) and involves all layers of the abdominal wall in the epigastrium, mesogastrium or hypogastrium (Figure 2). The bowel loops are almost always noted to be edematous and covered by a thick gelatinous matrix, the result of chemical peritonitis induced by exposure of the fetal intestine to urine after 30 weeks of gestation (WG).[23,24] Weight at birth on average is 2400-2500 g and gestational age is 36-37 WG. Intrauterine growth retardation (IUGR) and increased fetal mortality and morbidity may be associated with malabsorption or loss of fetal amino acids toward the amniotic fluid.[25,26] Occasionally, gastroschisis is associated with intestinal complications (10-20%).[23]

Patients with gastroschisis may have other associated primary congenital malformations (5-53%). It has been observed that such a large variation may be related to how the data are collected, whether it is a uni- or multicenter study and the country or geographic area where it is performed. For example, in Beijing, China it is associated with hydrocephalus and in Mexico with NTCD.[23, 27.28] Fetuses with gastroschisis also have an increased risk of prematurity (22-38%), symmetric IUGR (38-77%), oligohydramnios (36%) or to be aborted (7%).[29,30]

Epidemiology and Risk Factors

Although causes for gastroschisis are still poorly known, major risk factors involved are as follows.

Genetic Factors

The specific role of the genetic component in the etiology of gastroschisis is unclear. Although there are reports of

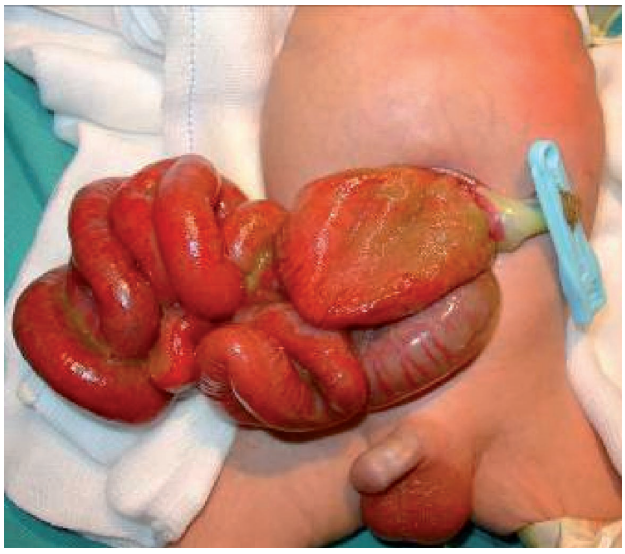

Figure 2. Newborn with gastroschisis. Note the right paramedian defect with protrusion of the ileum and stomach.

familial cases, gastroschisis occurs mostly as a sporadic event. It was observed that 4.7% of cases have at least one affected relative and the risk of recurrence is 3.5% among siblings.[31]

Torfs et al. analyzed 32 single nucleotide polymorphisms (SNPs) of candidate genes at risk for developing gastroschisis. This study identified a positive association for the gene NOS3 (nitric oxide synthase 3), ANP (atrial natriuretic peptide), ADD1 (alpha adducin 1) and ICAM1 (cell adhesion molecule 1).[32] These genes are related to mechanisms of angiogenesis, dermal and epidermal resistance and blood vessel integrity, which would support the hypothesis of vascular compromise in the etiology of gastroschisis.

The same authors also observed a strong interaction between allelic variants of these genes with maternal smoking because it increases the risk five times among subjects with one (heterozygous) or two (homozygous) variants of the gene: NOS3, ANP, ADD1 and ICAM1. The odds ratios (OR) of each gene for heterozygous and homozygous smoking mothers are shown in Table 1.[32]

It has been suggested that cadmium and CO_2 contained by the tobacco induce the expression of inflammatory factors such as TNF and NFK-β, activating NOS3 and ICAM1, which would be involved in gastroschisis pathophysiology.[33] The gene NOS3 encodes for nitric oxide 3 synthase, a membrane protein involved in second messenger and signal transduction pathways. When activated, this protein is translocated to the cytoplasm. Here it can convert arginine to nitric oxide (NO) and participate as a mediator of vascular tone, regulating endothelial cell migration in vascular remodeling and angiogenesis, while maintaining the integrins that are important in regulating cell migration. Tobacco would decrease the production of NO, inhibiting endothelial cell migration and capillary formation in endothelial cells of the umbilical vein, causing poor angiogenesis control and vascular remodeling, increasing the risk for gastroschisis. On the other hand, the ICAM-1 gene encodes for the intercellular 1 adhesion molecule, which modulates endothelial migration through the activation of NOS3 and the organization of actin in the cytoskeleton.[34]

There are several animal models through which gastroschisis study is carried out. In mice this pathology has been reproduced by exposure to various external agents such as radiation, carbon monoxide, ethanol, ochratoxin A, aflatoxin B, benzopyrene and medications such as ibuprofen and aspirin. There are also knockout mice (null) for the genes *pitx2*, *ap-2α*, *aebp1*, *aclp*, *alx-4*, *bmp-1* y *mab21-l2*, although it has been observed that mutations in these genes do not fully represent what happens in humans.[35]

In most cases gastroschisis occurs as an isolated defect (83.3-93%) but less frequently (12.2-35%) can also be part of other syndromes and/or chromosomal abnormalities. In the latter case, syndromes such as trisomy 13, 18, 21 and sex chromosome anomalies (1.2-3.7%) are included as well as other diseases: skeletal dysplasia, disruptive sequence, congenital amyoplasia, anomaly of Poland, Hanhart syndrome, partial or total colonic aganglionosis of the small intestine, biliary atresia, Hirschsprung disease, schizencephaly (0.7%) and multiple nonsyndromatic congenital anomalies (12.2%). Contrary to what occurs in isolated cases that are associated with young maternal age, cases with chromosomal abnormalities and multiple congenital anomalies are associated with advanced maternal age.[36,38]

Environmental Factors

The finding of discordant monozygotic and concordant dizygotic twins for gastroschisis suggests that environ-

Table 1. Associated genotypes

Gene and SNP	*Heterozygote*[1]	*Homozygote*[1]	*Hetero- and homozygote with current smoking habit*[1,2]
NOS3 7002G>T	1.9 (1.1–3.4)	1.2 (0.4–3.7)	5.2 (2.4–11.4)
ANP 553T>C	1.9 (1.0–3.4)	7.5 (1.7–33.5)	6.4 (2.8–14.6)
ADD1 1378G>T	1.5 (0.8–2.8)	4.9 (1.9–12.9)	4.3 (1.7–10.8)
ICAM1 778G>A	1.7 (1.0–3.2)	2.1 (0.4–10.3)	5.2 (2.1-2.7)

Modified from Torfs CP et al. Birth Defects Res A Clin Mol Teratol 2006;76:723-730. With permission of John Wiley & Sons, Inc.
[1]OR (95% CI).
[2]No significant differences reported between heterozygote and homozygote smokers.
SNP, single nucleotide polymorphism. OR, odds ratio; CI, confidence interval.

mental factors play an important role as a risk factor.[39] Those nongenetic factors found to be strongly associated with this malformation are presented below:

1. Maternal age—average age of mothers of children affected is 21.1 years. Women aged 14-19 are 7.2 times more likely to have a child with gastroschisis compared to those 25-29 years of age. Less than 7% of cases occur in mothers >29 years of age. This is the most consistent risk factor. The reason is unknown but is thought to be due to environmental exposure in this age group.[40]
2. Paternal age—fathers aged 20-24 are 1.5 times more likely to have a child with gastroschisis than those 25-29 years of age (OR 1.5, 95% CI 1.1-1.9).[5,40]
3. Ethnicity—Caucasian and Hispanic women aged 20-24 years have a higher risk of having children with gastroschisis (OR 2.5, 95% CI 1.4-4.5 and OR 1.5, 95% CI 1.1-2.0, respectively).[40]
4. Socioeconomic status—these factors include paternal absence (OR 4.0, 95% CI 1.4-11.5) and low income (OR 4.5, 95% CI 1.4-14.4).[5,40]
5. Parity—in contrast to initial reports, subsequent studies have not observed statistical effects regarding parity or gravidity.[40,41]
6. Exposure to drugs during pregnancy—drugs that significantly increase the risk are mainly analgesics and cold medicines such as aspirin (OR 4.7, 95% CI 1.2-18.1), ibuprofen (OR 4.0, 95% CI 1.0-16.0), pseudoephedrine (OR 2.1, 95% CI 0.8-5.5), phenylpropanolamine (OR 10, 95% CI 1.2-85), pseudoephedrine with paracetamol (OR 4.2) and nasal decongestants such as oxymetazoline and epinephrine (OR 2.4, 95% CI 1.5-2.4).[40,42]
7. Maternal smoking—approximately 42% of mothers of children with gastroschisis smoked during pregnancy. Malnourished mothers who smoked 3 months before or during the first trimester (>1 pack/day) have a very high risk (OR 26.5, 95% CI 7.9-89.4).[40,42]
8. Alcohol—intake during the first trimester increases the risk (OR 2.4, 95% CI 1.4-3.7).[40,42]
9. Illegal drugs—consumption during the first trimester increases the risk (OR 2.2, 95% CI 1.2-4.3). When limited to vasoconstrictor drugs such as cocaine, the OR is higher (OR 3.3, 95% CI 1.0-10.5). When it is combined with tobacco it increases (OR 2.1, 95% CI 1.0-4.4) and when tobacco consumption is intense, the risk is greater (OR 3.6, 95% CI 1.3-10.3).[5,40]
10. Nutritional factors—there is an association between BMI <18.1 kg/m^2 with gastroschisis (OR 3.2, 95% CI 1.4-7.4). Being overweight seems to have a protective effect (OR 0.2, 95% CI 0.04 to 0.8) as the risk decreases 11% for each BMI unit increase. The higher prevalence among young mothers may be related to a competition for essential nutrients between the mother, who is in a growth phase, and the fetus.[43]
11. Maternal infections—there is no association between the frequency of upper respiratory infections, fever and/or allergies, but there is with sexually transmitted infections and urinary tract infections during the first trimester of pregnancy (OR 4.0, 95% CI 1.4-11.6).[44]
12. Medical exposure—exposure to x-rays before or during the first trimester of conception presented an OR of 2.5 (95% CI 1.2-5.5).[3]
13. Occupational chemical exposure—there is an increased risk with exposure to solvents (OR 6.3, 95% CI 2.2-18.3).[40]
14. Other factors—it has been observed that women who change partners (change of paternity) in the index have an increased risk (OR 13.6, 95% CI 4.0-46.7). This is probably due to an autoimmune mechanism similar to what happens in some cases of preeclampsia. It has also been observed that short cohabitation time (time with the partner before the last menstrual period of pregnancy of the index case) represents a risk; when <1 year it has an OR 2.4 (95% CI 1.5-3.7) and is greater in multigravidas (OR 8.7, 95% CI 2.9-21.2). This is probably due to changes in lifestyle or lack of maternal time to produce tolerance to paternal antigens.[41]

Diagnosis

Gastroschisis is usually detected by ultrasound after 18 WG because before week 14, the process of physiological herniation of the mid-intestine has not been completed.[45-48] Measurement of AFP (α-fetoprotein) in maternal serum between 16-18 WG is useful for the detection of abdominal wall defects and the acetylcholinesterase/pseudocholinesterase index to distinguish wall defects such as gastroschisis with NTCDs.[31]

When the fetus dies, it is important to perform a necropsy to assess the size and location of the defect, both of the umbilical ring and the presence or not of primary

or secondary associated anomalies and to evaluate the structure and integrity of the abdominal wall and assess the amniotic epithelium in search of lipid vacuoles. The latter are characterized by being composed of triglycerides and cholesterol esters with an "unusual" pattern of fatty acids because they are rich in palmitic and palmitoleic acid and lacking in essential fatty acids. It has been suggested that these vacuoles may be a consequence of different dietary factors involved in gastroschisis pathogenesis and, in addition, allow the differentiation of gastroschisis from other defects of abdominal wall closure such as omphalocele.[29,49] Cytogenetic and/or molecular analysis is not indicated for cases of isolated gastroschisis.[50]

Treatment and Prognosis

Multidisciplinary pre- and postnatal management is required. Controversy remains today regarding the timing and route by which delivery should be performed. It is known that elective termination via cesarean section after 36-37 WG and before the onset of labor prevents passage through the birth canal, which decreases the risk of contamination with bacterial flora and mechanical damage in the viscera. However, a significant difference has not been shown in terms of complications or survival.[30] Definitive treatment is surgical. The timing and technique for surgical closure depends on the degree of intestinal inflammation, size of the defect and the newborn's general condition.[51-54] Primary surgical closure before 24 h after birth (extrauterine life, EUL) is preferred, but if there is viscero-abdominal disproportion (present in 20-49% of cases), gradual reduction with silo is necessary to avoid complications. Surgical repair should be performed between 6 and 10 days of EUL.[55] Exchange of amniotic fluid to reduce inflammatory mediators has not shown any benefit.[56] In general, the prognosis is good with a survival ≥90%, but in developing countries the risk of death may be as high as 50-60%. The leading causes of mortality are related to prematurity, neonatal sepsis, intestinal complications related to intestinal ischemia, acute renal failure or multiple organ failure.[32,57] Of patients diagnosed prenatally, 10% die at this stage and elective termination of pregnancy is performed in 26.5% of cases.[49]

Differential Diagnoses

It has been determined that up to 20% of patients with abdominal wall defects are misdiagnosed as gastroschisis. The differential diagnosis of omphalocele, bladder exstrophy, limb body wall complex, amniotic band syndrome, ectopia cordis and pentalogy of Cantrell must be established.[31] If one takes into account the clinical features mentioned above, it is relatively easy to establish the correct diagnosis of gastroschisis. Gastroschisis is a congenital defect of the abdominal wall with a significant increase in incidence worldwide in recent years, particularly in Mexico. To date, there are six different theories to explain the development of this malformation. The hypothesis that proposes "the escape of the yolk sac" is the most current and accepted. A pattern of multifactorial inheritance with genetic risk factors and environmental issues is involved. Among the most important genetic factors are homozygous polymorphisms of genes ANP (553T>C) and ADD1 (1378G>T). It has been observed that both genotypes interact significantly with maternal smoking. Among the environmental factors, history of maternal age, exposure to drugs (particularly phenylpropanolamine), solvents, maternal smoking and change in paternity stand out. Future studies with adequate study design will allow determination of the risk factors associated with this congenital malformation in our population, which will lead to the development of novel and improved strategies for diagnosis and prevention.

Finally, it is important to inform all pregnant women, especially those of young age, to avoid being exposed to the agents mentioned and emphatically insist about the importance of no smoking during pregnancy.

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