



## Gastroesophageal reflux and congenital gastrointestinal malformations

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### Abstract

Although the outcome of newborns with surgical congenital diseases (e.g., diaphragmatic hernia; esophageal atresia; omphalocele; gastroschisis) has improved rapidly with recent advances in perinatal intensive care and surgery, infant survivors often require intensive treatment after birth, have prolonged hospitalizations, and, after discharge, may have long-term sequelae including gastro-intestinal comorbidities, above all, gastroesophageal reflux (GER). This condition involves the involuntary retrograde passage of gastric contents into the esophagus, with or without regurgitation or vomiting. It is a well-recognized condition, typical of infants, with an incidence of 85%, which usually resolves after physiological maturation of the lower esophageal sphincter and lengthening of the intra-abdominal esophagus, in the first few months after birth. Although the exact cause of abnormal esophageal function in congenital defects is not clearly understood, it has been hypothesized that common (increased intra-abdominal pressure after closure of the abdominal defect) and/or specific (e.g., motility disturbance of the upper gastrointestinal tract, damage of esophageal peristaltic pump) pathological mechanisms may play a role in the etiology of GER in patients with birth defects. Improvement of knowledge could positively impact the long-term prognosis of patients with surgical congenital diseases. The present manuscript provides a literature review focused on pathological and clinical characteristics of GER in patients who have undergone surgical treatment for congenital abdominal malformations.

**Key words:** Gastroesophageal reflux; Congenital diaphragmatic hernia; Esophageal atresia; Omphalocele; Gastroschisis

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**Core tip:** Although the outcome of newborns with surgical congenital diseases has improved rapidly with recent advances in perinatal intensive care and surgery, infant survivors often may have long-term sequelae including, above all, gastroesophageal reflux (GER). Common or specific pathological mechanisms may play a role in the etiology of GER in patients with birth defects. The improvement of knowledge of long-term outcome and follow-up could positively impact the long-term prognosis of newborns with surgical congenital diseases. The present manuscript provides a literature review focused on pathological and clinical characteristics of GER in patients who have undergone surgical treatment for congenital abdominal malformations.

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## GASTROESOPHAGEAL REFLUX

Gastroesophageal reflux (GER) is defined as the involuntary retrograde passage of gastric content into the esophagus, with or without regurgitation or vomiting<sup>[1]</sup>. GER is a well-recognized condition in infants, which usually resolves after physiological maturation of the lower esophageal sphincter (LES) and lengthening of the intra-abdominal esophagus in the first few months after birth<sup>[2-4]</sup>. The incidence of GER in infants is 85%, occurring 1.6 times more frequently in males than in females<sup>[1]</sup>. Prevalence of GER decreases to 18% in childhood<sup>[1]</sup>. This condition is markedly less common in adult subjects<sup>[5,6]</sup>. Generally, it is classified into: (1) "primary"; (2) "secondary"; and (3) "acquired" GER. Primary GER results from a functional disorder of the proximal digestive tract, whereas secondary GER includes structural, infectious, metabolic, neurological and allergic disorders which cause the passage of gastric contents into the esophagus<sup>[7]</sup>. Despite the fact that the majority of GER cases are independent of congenital gastrointestinal malformations, acquired GER can also be due to, or favoured by congenital anomalies<sup>[8]</sup> (Table 1); it has been reported that GER is commonly associated with birth defects. Although the exact cause of abnormal

esophageal function in congenital defects is not clearly understood, it has been hypothesized that common (increased intra-abdominal pressure after closure of the abdominal defect) and/or specific (*e.g.*, motility disturbance of the upper gastrointestinal tract, damage of esophageal peristaltic pump) pathological mechanisms may play a role in the etiology of GER in patients with birth defects. Moreover, associated anomalies, mental retardation or neurological impairment after prematurity or chromosome abnormality may further increase the risk of GER in these pediatric populations<sup>[9]</sup>. In accordance with these data, a high frequency of gastroesophageal long-term complications (*e.g.*, dysphagia, esophageal strictures, esophagitis, esophageal metaplasia and esophageal carcinoma), failure to thrive, as well as respiratory symptoms has been observed, compared to healthy controls<sup>[10,11]</sup>. Additionally, pathological findings were found in a high number of patients through endoscopy, manometry and pH-measurements<sup>[10,12,13]</sup>. However, it must also be remembered that literature results are heterogeneous and often report opposing outcomes. This is likely due to different inclusion criteria of patients, lack of correlation in neonatal variables, non systematic assessments, and heterogeneous therapeutic protocols used<sup>[14]</sup>.

Hence, we wish to summarize what is currently known on pathological and clinical characteristics of GER in surgically-treated patients with congenital gastrointestinal malformations.

## GER AND CONGENITAL DIAPHRAGMATIC HERNIA

Congenital diaphragmatic hernia (CDH) is a rare (1 per 2500 births) anomaly of the diaphragm, typically characterized by abdominal organ herniation into the chest cavity<sup>[15]</sup>. In 84% of cases, the defect is located on the left side of the diaphragm<sup>[16]</sup>. Right-sided and bilateral CDH, which occur in 14% and 2% of cases, respectively, are associated with a worse prognosis<sup>[16]</sup>. Several hypothesis have been proposed to explain the embryologic events leading to CDH, and several genetic (*e.g.*, structural abnormalities of chromosomes, aneuploidies, genetic syndromes)<sup>[17]</sup> and environmental (impaired retinoic acid pathway)<sup>[11]</sup> factors may play a role in the development of CDH. CDH can present as an isolated defect or in combination with other congenital anomalies<sup>[18]</sup> and includes pulmonary, neurological and gastro-intestinal, especially GER, comorbidities. GER is a common complication in CDH survivors and incidence is 20%-84% during the first year of life<sup>[19]</sup>. A prevalence of 63% was reported in adult survivors of CDH, co-existing with Barrett's esophagus in 54%<sup>[20,21]</sup>. The mechanisms responsible for GER in CDH survivors have not been clarified and several theories have been proposed. Esophageal dysmotility and ectasia, maldevelopment or weakness of the

**Table 1** Incidence of gastroesophageal reflux in children and adults affected by gastrointestinal congenital defects

Congenital defects	Incidence GER in childhood	Incidence GER in adulthood
Congenital diaphragmatic hernia	20%-84% Arena 2008	20% Koivusalo 2005
Esophageal atresia	50% Koivusalo 2007	45% Ijsselstijn 2013
Omphalocele	50%-70% Beaudoin 1996	Equal to healthy subjects Koivusalo 1999
Gastroschisis	50%-70% Beaudoin 1996	Equal to healthy subjects Koivusalo 1999
Intestinal malrotation	79% Jolley 1985	1.2% Nehra 2011

GER: Gastroesophageal reflux.

crura, shortening of the esophagus, disruption of the angle of His, intestinal malrotation, and a higher intra-abdominal pressure after surgical repair are possible explanations of GER in CDH<sup>[22]</sup>. Additionally, the diaphragmatic sling may be malformed or absent, and repair changes the anatomy of the region. Moreover, abnormality of the esophageal dimensions might also contribute to development of GER. This pathological condition might be congenital or acquired, resulting from extrinsic pressure on the mediastinum exercised by the herniated viscera<sup>[23]</sup>. Furthermore, malrotation may delay gastric emptying, and the abnormal balance of pressures in the thorax and abdomen, during respiratory cycle, facilitates retrograde passage of gastric contents to the esophagus<sup>[24]</sup>. There is evidence of abnormal enteric innervation in CDH and it is likely that esophago-gastric peristalsis is impaired<sup>[25]</sup>. Finally, studies reported that preoperative thoracic position of the stomach and/or an inappropriate intra-abdominal position or volvulus of the stomach after surgical treatment could cause intragastric stasis of food and, therefore, GER<sup>[26,27]</sup>.

Several authors have attempted to define clinical variables that may predict GER. A significant relationship has been found between duration of ventilatory support and GER<sup>[20,28]</sup>. Postoperative intolerance of enteral feedings and prolonged hospitalization were also found predominantly in patients with GER<sup>[20]</sup>. Finally, size of diaphragmatic defect and use of prosthetic patch could influence incidence of GER in CDH patients<sup>[29]</sup>. GER can complicate pre-existing respiratory disease and, in the light of abovementioned pathological pathways, responds poorly to medical treatment<sup>[25]</sup>. However, authors reported satisfactory improved clinical parameters in patients treated conservatively by maintaining supine position, by frequent administration of small amounts of oral nutrition, and by medical treatment<sup>[30-32]</sup>. Antireflux surgery may be an option for patients after failed medical therapy, although long-term success rate of this procedure has yet to be proven<sup>[33]</sup>. A prophylactic fundoplication has also been proposed in patients with CDH<sup>[34]</sup>. Up to 23% of

affected newborns exhibiting an intrathoracic position of the liver need such surgical correction<sup>[14]</sup>. However, it is difficult to accurately compare results of studies conducted on GER-related CHD as many aspects of the disease are still unknown and, additionally, each study varies regarding CDH severity, postoperative CDH management and follow-up period. Furthermore, predictive factors for late GER could not be identified and screening for early GER does not protect from future GER; therefore, long-term follow-up for GER in CDH survivors is mandatory<sup>[30,35-37]</sup>.

## GER AND ESOPHAGEAL ATRESIA

Esophageal atresia (EA) is the most common esophageal malformation; incidence is 1 in 3500 live births<sup>[38,39]</sup>. Classification of EA anomalies is determined by the location of the atresia and by the presence of any associated fistula to the trachea. Five different variants have been clinically described. The primary types of congenital EA are: EA with distal tracheoesophageal fistula (TEF) (85%, Vogt IIIb, Gross C), isolated EA without TEF (8%, Vogt II, Gross A), TEF without atresia or H-type TEF (4%, Gross E), EA with proximal TEF (3%, Vogt III, Gross B) and EA with proximal and distal TEF (< 1%, Vogt IIIa, Gross)<sup>[40,41]</sup>. The outcome following EA/tracheoesophageal fistula (EA/TEF) repair is variable. Some patients have an uneventful postoperative period, while others reported several complications that can significantly affect their health through adulthood, including GER. GER is so often recognized in survivors of neonatal repair of esophageal atresia and tracheoesophageal fistula (EA/TEF) that it has become a component of this malformation: approximately 50% of these patients had GER during infancy<sup>[42]</sup>, and this proportion tends to increase over time<sup>[43]</sup>. The presence of GER is generally believed to be due to an intrinsic deficiency in the motor function of the stomach and/or esophagus<sup>[44]</sup>. Authors assessed that delayed gastric emptying and antral hypomotility, important factors predisposing to GER, are frequent in long-term follow-up of patients operated on for EA-TEF<sup>[45,46]</sup>. Esophageal dysfunction has also been reported after successful repair of EA in 20 newborns with EA by recording intraluminal pressure of both proximal and distal segments<sup>[47]</sup>. In addition, abnormal motility might affect esophageal clearance, resulting in abnormal bolus clearance, decreased clearance of refluxed materials, dysphagia, severe mucosal damage, esophagitis and, possibly, esophageal carcinoma<sup>[48]</sup>. It is likely that GER is exacerbated by surgical repair and gastrostomy, causing an alteration of the anatomical gastro-esophageal junction and the angle of His<sup>[49-51]</sup>. Esophageal anastomosis under tension displaces the gastroesophageal junction upwards, diminishing the efficiency of the antireflux barrier<sup>[52]</sup>. The esophageal peristaltic pump, another antireflux barrier, is also

damaged in EA/TEF due to deficient arrangement of the muscle layers and damage to the innervation of the repaired esophagus. Moreover, extrinsic innervation by branches of the vagus and laryngeal nerves, and also intrinsic innervation, are congenitally deficient in EA<sup>[53]</sup>. In addition, gastrostomy, sometimes used in the treatment of EA/TEF, facilitates GER<sup>[54]</sup>. Finally, tracheomalacia and/or tracheal stenosis, which are relatively common in EA/TEF newborns, cause airway obstruction and induce GER by exaggerating negative inspiratory force and increasing the abdomino-thoracic pressure gradient<sup>[53]</sup>. However, to date, it is unclear if these abnormalities exist immediately after EA repair or if they develop over time. Although studies suggest that motility disorders are also present in esophageal atresia before surgery<sup>[47]</sup>, published studies do not allow us to conclude whether GER is congenital (abnormal innervation)<sup>[55]</sup> or acquired due to inevitable damage during surgical reconstruction<sup>[56]</sup>.

Although GER manifests itself by vomiting, failure to thrive, and respiratory symptoms, it has been shown that symptoms of GER and histologic findings are poorly correlated, raising doubts regarding correct management. Generally, a post-operative long-term endoscopic and pH-metric follow-up of all patients is warranted. Endoscopic follow-up is recommended for all surgically treated patients irrespective of symptoms. Endoscopic follow-up of children with completely normal esophageal biopsies can be discontinued at 3 years of age. In patients with mild esophagitis, routine follow-up should be extended to at least 6 years of age<sup>[43]</sup>. As EA/TEF newborns with GER do not benefit from postural, dietary or prokinetic treatments<sup>[57]</sup>, primarily surgery may be required, especially in the case of refractory anastomotic stenosis, pure and long-gap EA, and duodenal atresia<sup>[58]</sup>. Patients who have undergone anti-reflux surgery should also be followed long-term<sup>[43,59]</sup>. Nevertheless, some authors refuse to perform fundoplication as esophageal motility, in these children, is poorly known. Moreover, to date, there is no randomized trial that has evaluated treatment of GER in children with EA with fundoplication vs. acid suppressive medication<sup>[60]</sup>. Certainly, several studies have shown that the persistence of GER might increase the risk of long-term complications, such as dysphagia, esophageal strictures, esophagitis, esophageal metaplasia and esophageal carcinoma in children and adults born with EA compared to healthy controls<sup>[61]</sup>. In conclusion, there are no well-outlined algorithms for medical and/or surgical therapy. Standardized protocols and reliable reporting are necessary to develop guidelines to better manage postoperative GER in EA/TEF patients<sup>[62,63]</sup>.

in infants with congenital abdominal wall defect (CAWD), including omphalocele and gastroschisis<sup>[64,65]</sup>. Incidence of GER in these patients has been reported to be between 50% and 70%<sup>[66]</sup>. Moreover, associated anomalies (*e.g.*, esophageal atresia, duodenal atresia and diaphragmatic hernia), chromosome abnormality, and neurological impairment can strongly increase the likelihood of GER<sup>[9]</sup>. Although it has been hypothesized that the etiology of GER in patients with CAWD is both related to increased intra-abdominal pressure after the closure of the abdominal defect and gastrointestinal motility disturbance<sup>[67]</sup>, the etiology of GER related to omphalocele or gastroschisis is still under study.

Omphalocele, a ventral defect of the umbilical ring resulting in herniation of the abdominal viscera, is one of the most common congenital anterior abdominal wall defects. It occurs in 1 in 3000 to 10000 live births<sup>[68]</sup> and is characterized by the absence of abdominal muscles, fascia, and skin due to the defective closure of the abdominal wall in the embryo before 9 weeks of gestation. The malformation causes herniation of the abdominal contents, covered by a membranous sac consisting of peritoneum and amnion, into the base of the umbilical cord<sup>[69]</sup>. In infants with omphalocele, the incidence of GER considerably exceeds that of control group children<sup>[70]</sup>. It is hypothesized that in patients with a large omphalocele and severely underdeveloped abdominal cavity, GER is favored by the high postoperative intra-abdominal pressure after repair of the defect<sup>[71]</sup>. Furthermore, Beaudoin *et al.*<sup>[66]</sup> reported that infants affected by large omphaloceles had an increased risk of GER, especially where primary closure with skin or silo only was possible. A high incidence of GER in omphalocele patients was described above all during the first few years of life; it appears that GER clearly improves after infancy and, later childhood symptoms are less marked and easily controlled with medication<sup>[70]</sup>. In light of these data, routine diagnostic workup (endoscopy and pH monitoring) for GER is warranted for children with omphalocele during the first year of life. If GER is diagnosed, medical treatment should be started and long-term follow-up might be arranged if it persists. Additionally, older patients with omphalocele should undergo GER evaluation in the presence of GER-related symptoms<sup>[70]</sup>.

Gastroschisis is defined as an extraumbilical herniation of bowel without covering sac through an anterior abdominal wall defect. It occurs in about one in 600 live births<sup>[71]</sup>. Gastroschisis could be the result of amniotic damage, possibly from some as yet unidentified toxin. Further bowel damage can be explained by the subsequent mesenteric injury<sup>[72]</sup>. Infant mortality with gastroschisis has been markedly reduced in the last decade by new surgical techniques, improved metabolic monitoring, and total parenteral nutrition. On the other hand, to date, late complications of gastroschisis are emerging as clinical problems, with the longer survival of affected newborns. Some gastrointestinal complications, such as GER, have been described<sup>[70]</sup>. To date, it is not clear

## GER AND CONGENITAL ABDOMINAL WALL DEFECTS: OMPHALOCELE AND GASTROSCHISIS

GER is considered a common pathological finding

if evidence of reflux stems from failure of the lower esophageal sphincter (LES) or from problems that “look like” GER<sup>[71]</sup>. However, Koivusalo *et al.*<sup>[70]</sup> reported that, in infants with gastroschisis, when normal bowel motility was surgically restored, the prevalence of GER did not exceed that of healthy children. In gastroschisis, GER may be secondary to operative reduction of the bowel which, in turn, can distort the stomach and the angle of His, suggesting one cause for a major incidence of reflux in these infants<sup>[73]</sup>. In addition, clinical and experimental models supported evidence that intestinal dysmotility may contribute to GER and to formation of hiatal hernia. Recently, a study has described a high incidence of associated hiatal hernia in gastroschisis patients. The presence of large associated hiatal hernia is correlated with severe GER, delayed feeding, requirement for antireflux surgery, and a prolonged hospital stay. Although the role of dysmotility in GER-related gastroschisis has not been clearly defined<sup>[74-76]</sup>, Jadcherla *et al.*<sup>[77]</sup> reported impaired feeding milestones, basal pharyngoesophageal peristaltic failure and less frequent peristaltic reflexes of the upper and lower esophageal sphincters in neonates with gastroschisis. In an experimental model, a decreased number of interstitial cells of Cajal (intestinal pacemaker cells) have been found, and neuronal abnormalities might further justify intestinal dysmotility<sup>[77,78]</sup>. Additionally, authors assessed that animal models, with carbonylpeptidase-like protein deficiency, had a very similar abdominal wall defect to human gastroschisis and also exhibited absence of intestinal pacemaker cells and delayed neuromuscular development<sup>[79]</sup>.

The clinical course of GER-related to gastroschisis is still unclear<sup>[80]</sup>. Patients with gastroschisis should undergo GER evaluation only in the presence of GER-related symptoms<sup>[70]</sup>. Koivusalo and collaborators reported that in CAWD patients, compared to a general population, the quality of life and morbidity from acquired disorders are similar and rarely cause serious problems<sup>[71]</sup>. Conversely, in the presence of large hiatal hernia (II or III type), with severe, medically refractory GER, this selected patient population might require antireflux surgery<sup>[81,82]</sup>.

## GER AND INTESTINAL MALROTATION

Intestinal malrotation (IM) is defined as an anomaly of rotation and fixation of the midgut<sup>[83]</sup>. Malrotation of the intestinal tract is a product of a well-defined aberrant embryology. It usually occurs due to incomplete rotation or a complete failure of rotation of the primitive intestinal loops around the superior mesenteric artery axis in the fetal period<sup>[84]</sup>. IM is found either alone or in combination with other congenital anomalies, including CHD and CAWD<sup>[85]</sup>. IM is a rare disorder, found in only approximately one per 10000 individuals. However, the incidence

of IM in infants and children beyond the neonatal period is difficult to estimate, as such anomalies may remain asymptomatic and undetected throughout life. Approximately 50% to 70% of cases are diagnosed during the neonatal period; about 50% present in the first week of life, and over 60% present before the end of the first month<sup>[86,87]</sup>. Male infants are more frequently affected than female infants<sup>[88]</sup>. Wang *et al.*<sup>[89]</sup> classified IM into four categories: non-rotation, malrotation, reversed rotation, and paraduodenal hernia. Due to the lack of normal intestinal mesenteric fixation, IM may present with acute or chronic symptoms. Acute symptoms are due to duodenal obstruction, with or without midgut volvulus, and sudden infant death. Chronic symptoms, due to intermittent intestinal obstruction, include abdominal pain, bloating or constipation, postprandial fullness, epigastric discomfort, early satiety, and GER<sup>[90]</sup>. The association between GER and IM has been well described. In a series of 74 children undergoing Nissen fundoplication for persistent GER unresponsive to intensive medical treatment, there was an unexpectedly high incidence of IM<sup>[91]</sup>. Moreover, the high incidence of GER and the significant improvement after correction of malrotation further show the relationship between delayed gastric emptying and GER<sup>[92]</sup>. In light of these data, delayed or impaired gastric emptying in IM are thought to be contributing factors in the development of GER. Using gastric emptying studies and esophageal pH monitoring, authors assessed that gastric dysmotility and esophageal pH abnormalities were highly prevalent in children with malrotation compared with children only affected by isolated GER<sup>[93]</sup>. It has been hypothesized that, in infants with IM, reversed gastric peristaltic waves, especially during fetal development lead to defects of the plexus myentericus, favouring GER<sup>[85]</sup>. In addition, the high prevalence of GER in infants affected by IM suggests that an impaired gastroesophageal junction may result from the same embryological defect that leads to the interference of normal intestinal rotation and fixation during fetal development<sup>[85]</sup>. Conversely, no sufficient literature data supported the mechanical gastric-outlet obstruction as a factor promoting GER; a high GER prevalence persisted despite the relief of gastric-outlet obstruction with a successful Ladd operation<sup>[90,94]</sup>.

Generally, the course of treated infants with GER and IM depends on the presence or absence of symptoms to suggest GER. The course in symptomatic newborns is similar to infants with GER without IM, thus, their outcomes are related to reflux pattern type<sup>[67]</sup>. Conversely, asymptomatic patients with GER have a better prognosis. However, these latter might continue to have GER, during follow-up, favouring Barrett esophagus in children<sup>[85,95]</sup>. Therefore, the high prevalence of GER in infants with IM requires careful evaluation and follow-up.

## CONCLUSION

Despite the fact that the majority of GER cases are independent of congenital gastrointestinal malformations, GER is most common in patients with congenital gastrointestinal diseases<sup>[5,6]</sup>. GER can further worsen birth defects and favour the onset of related comorbidities, constituting the most prevalent complication in long-term follow-up<sup>[96,97]</sup>. However, to date, long-term outcome and follow-up data after surgical repair are limited. Improvement of knowledge could positively impact the long-term prognosis of these patients who, benefiting from a more intensive follow-up program, would avoid gastroenterological symptoms and/or comorbidities during adulthood. Additionally, this might lead to an era of "individualised" management, identifying specific selection criteria for medical and/or surgical treatment, especially for younger children with longer life expectancy<sup>[98-100]</sup>.

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