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A proposed classification system for familial intestinal atresia and its relevance to the understanding of the etiology of jejunoileal atresia

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Abstract Familial cases of the various types of intestinal atresia are well described, and we now report an additional family. Based on a review of the literature, a classification system for the different types of familial atresia is presented. Current teaching attributes most jejunoileal atresias to in utero vascular accidents occurring relatively late in gestation (after the 11th or 12th week). Although some cases clearly occur this way, as a result of processes such as volvulus and intussusception, knowledge of the familial form of the disease indicates that most cases of jejunoileal atresia actually result from disruption of a normal embryologic pathway, most likely the development of the superior mesenteric artery and its branches. They should be considered to be true embryologic malformations rather than acquired lesions.

Since the work by Louw and Barnard [1,2] in the 1950s, most cases of jejunoileal atresia have been ascribed to "in utero vascular accidents," and the lack of associated anomalies and the presence of meconium, squamous epithelial cells, lanugo hair, or bile droplets distal to the atresia have been interpreted as evidence that these are late events (after the 11th or 12th week of fetal life) [3]. In this model, these lesions are acquired rather than being true embryonal malformations.

Although there is no disputing this mechanism for atresias that result from in utero volvulus or intussusception or those associated with gastroschisis, the theory still begs the question as to what causes the obliteration of the mesenteric vessels in the cases of atresia that are not attributable to one of these proven pathologic processes. The classic mechanisms of acute vascular occlusion, embolism, local thrombosis, and arteritis, are unlikely to be responsible because it is impossible to envision a scenario by which any of these processes would or could be restricted to the mesenteric circulation and would not result in more widespread fetal anomalies.

In the half century since Louw and Barnard published their work, there has been an ever-increasing number of reports of familial cases of the various types of intestinal atresia. Although they are rare, the study of these cases is likely to increase our understanding of the nonfamilial cases as well because even in cases where a gene is not abnormal, knowledge of the gene's existence and action defines a specific embryologic pathway that, if disrupted by whatever mechanism, genetic or otherwise, will produce the abnor-

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mality in question. We now report an additional case of familial small intestinal atresia, and based on this case and a review of the literature, propose a classification of the types of familial gastrointestinal atresia and discuss the implications of this classification in elucidating the etiologic mechanisms involved in both familial and nonfamilial patients, with particular emphasis on the etiology of atresias of the jejunum and ileum.

1. Case report

A boy was born at 35 weeks gestation with a birth weight of 2065 g. Mild respiratory distress was noted shortly after birth. An orogastric tube failed to pass into the stomach, stopping at the thoracic inlet, and an abdominal x-ray showed evidence of a high jejunal obstruction. He was diagnosed as having proximal esophageal atresia with a distal tracheoesophageal fistula and a high jejunal atresia. Laparotomy was performed at around 24 hours of life. An apple peel atresia (type IIIb) was present, with the proximal atresia at the duodenojejunal junction. An additional type I atresia was present in the distal segment, and malrotation was present. An end-to-end anastamosis was performed proximally, the distal web was excised, and a gastrostomy was placed.

It was planned to return him to the operating room the following day to repair the esophagus, but this was not done because of the development of thrombocytopenia, which persisted despite the absence of other signs of sepsis. On postoperative day 5, bilious drainage was noted from the abdominal wound, and he was reexplored. There was complete dehiscence of the proximal anastamosis, with diffuse peritonitis. A tube duodenostomy was created, and the proximal end of the distal segment was brought out as an ostomy. Blood cultures grew a resistant *Klebsiella*, and peritoneal cultures grew *Escherichia coli*. After resolution of the sepsis, at 3 weeks of age, he returned to the operating room. The tracheoesophageal fistula was ligated, but anastamosis of the esophagus was not possible because of the length of the gap.

Tube feeds were instituted into the ostomy, and the drainage from the duodenostomy tube was mixed with them. However, adequate nutrition could never be achieved through the gastrointestinal route, and the patient developed progressive total parenteral nutrition cholestasis. In addition, he experienced multiple, serial, Gram-negative, and fungal infections, only some of which were central catheter-related. These almost continual infections prevented any further surgical attempts to reconstruct either his esophagus or intestinal tract. Abnormal thyroid function tests were noted, and he was started on replacement therapy. The hepatic dysfunction progressed, and at 4 months of age, he died of sepsis and resulting multiorgan failure.

The older and only sibling of this infant had been born at another hospital three and a half years previously. He was found to have either a type I or a short type II jejunal atresia, which was successfully repaired.

2. Discussion

Our case fits in most respects with previous reports of familial apple peel atresia. However, the coexistence of esophageal atresia has not been reported before, and, in fact, we are only aware of one report of this association in a nonfamilial case [4]. This rarity indicates that the association is most likely to be just a chance event. Although unproven, the multiple and almost continual infectious episodes seen in our patient suggest the possibility of an immune defect. Immune defects have been described in several patients with various types of familial bowel atresia [5-7] but not, to our knowledge, in any other patients with the apple peel type. If an immune defect exists, it could be a separate primary abnormality or might just be the result of deficient development of the immune function of the gut as a consequence of the atresia.

A review of the literature indicates that familial cases of gastrointestinal atresia can be divided into 5 distinct types, all of which have a nonfamilial counterpart.

2.1. Class 1

Pyloric atresia (also includes cases of antral atresia and atresia of the very proximal duodenum) [8-12]: Inheritance is in an autosomal recessive manner, and there are no atresias at other levels. The association of pyloric atresia with epidermolysis bullosa in some cases is well known [13-15], and this syndrome also shows autosomal recessive inheritance, but, as it is unlikely that the mechanism leading to an abnormal pylorus is the same, these patients are not part of this discussion.

2.2. Class 2

Duodenal atresia [16-18]: Inheritance is in an autosomal recessive manner, and the atresia is located in the second or third portion of the duodenum, as opposed to cases where the atresia is at the duodenojejunal junction (see below). There are no other atresias at other levels and no associated chromosomal or structural anomalies.

2.3. Class 3

Hereditary multiple atresia syndrome [19-28]: This was first identified in a French-Canadian population in the Lake St. John region of Quebec and has since been also identified elsewhere. It is inherited in an autosomal recessive manner, and the atresias can occur anywhere along the length of the gastrointestinal tract, from the stomach to the rectum. Characteristic findings in this disorder include intraluminal calcifications and, microscopically, sieve-like multiple intestinal lumina. There may be cystic dilatation of the bile