Association of Gastric Heterotopic Pancreas and Esophageal Atresia in Children

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ABSTRACT

Objectives: Esophageal atresia with or without tracheo-esophageal fistula is a frequent malformation that occurs in about 1 of 3000 live births. It can be associated with other congenital malformations. The aim of this study was to measure the frequency of heterotopic pancreas (HP) in children with esophageal atresia (EA) and to evaluate possible linkage with other malformations.

Materials and Methods: All patients with EA were prospectively followed since 2005 at Hôpital Sainte-Justine and since 2006 at the Montreal Children's Hospital. We compared 91 patients who underwent gastroscopy during that period with 182 control patients who submitted to gastroscopy for other indications. The presence or the absence of HP and its localization were noted in both groups. The following data were also collected on patients with EA: sex, gestational age, EA type, and other malformations.

Results: Seventeen (18.7%) of the 91 patients with EA had gastric HP compared with 1 (0.5%) in the control group (OR 42, 95% confidence interval 7–249, $P < 0.001$). There were no differences between patients with or without HP regarding sex, prematurity, EA type, and the presence or absence of other congenital abnormalities.

Conclusions: This study demonstrates, for the first time, that gastric HP is associated with EA irrespective of other malformations.

Key Words: esophageal atresia, heterotopic pancreas, tracheo-esophageal fistula

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Esophageal atresia with or without tracheo-esophageal fistula (EA-TEF) occurs in about 1 in 3000 live births (1). Five EA-TEF types have been described, and type C, the most frequent, encompasses EA with distal TEF (2). EA-TEF can be associated with prematurity secondary to polyhydramnios and other congenital malformations in more than 50% of patients. One fourth of these abnormalities are related to the gastrointestinal tract, including anorectal anomaly, duodenal and jejuno-ileal atresia, malrotation, and duplication (3).

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Heterotopic pancreas (HP) is defined as pancreatic tissue lacking anatomical and vascular continuity with the pancreatic gland. It has been reported in adults in 1% to 2% of autopsies and is most commonly located in the antrum, duodenum, jejunum, and Meckel diverticulum (4,5). Classically, it is described as a submucosal mass with central umbilication measuring about 2 mm to 4 cm (Fig. 1). The aim of this study was to assess the frequency of HP in children with EA-TEF and to determine whether other malformations are associated with HP.

MATERIALS AND METHODS

Patients with EA-TEF were prospectively followed at multidisciplinary EA-TEF clinics since 2005 at Hôpital Sainte-Justine and since 2006 at the Montreal Children's Hospital. In both hospitals, the follow-up protocol of patients with EA-TEF includes at least 1 endoscopy in the first 2 years of life, and then every 3 to 5 years or sooner if needed. Among patients studied at the 2 clinics ($n = 112$), we reviewed all children with EA-TEF who underwent gastroscopy between January 2006 and September 2008. To compare the frequency of HP with a general pediatric population attending a gastroenterology clinic, we assessed every patient with EA-TEF in relation to 2 control patients without EA-TEF who underwent gastroscopy for other indications. The control patients were arbitrarily chosen from archived gastroscopy procedures in the 2 pediatric gastroenterology divisions. Because the archives are classified alphabetically according to last name, we chose patients preceding and following the ''case'' patients. All of the patient and control names were anonymous, with a number assigned to each of them. The presence or the absence of HP and its localization were noted for all of the patients and controls. We also reviewed all of the pictures taken during the endoscopy procedures, if available.

Statistical analyses were performed with SPSS (SPSS, Chicago, IL). Fisher exact test was used to analyze categorical variables for 2 independent groups. We compared the EA-TEF group with the control group for the presence or absence of HP. We also evaluated the EA-TEF group with and without HP for different characteristics: sex, gestational age younger than 37 weeks, EA-TEF type, and other malformations. The study was approved by the institutional boards of both hospitals.

RESULTS

Between January 2006 and September 2008, 91 children studied at the EA-TEF clinics of the 2 hospitals underwent at least 1 endoscopy. Their last endoscopy was compared with 182 control patients without EA-TEF. Demographics of patients and controls are presented in Table 1. Seventeen of the 91 patients with EA-TEF (18.7%) had an HP (Fig. 1) compared with 1 (0.5%) in the control group (OR 42, 95% confidence interval 7–249, $P < 0.001$) (Table 1). Eighty-eight percent of the endoscopies were photographed to visualize HP. All of the HPs were localized in the stomach, 16 of them specifically in the antrum. Twenty-nine patients with EA-TEF

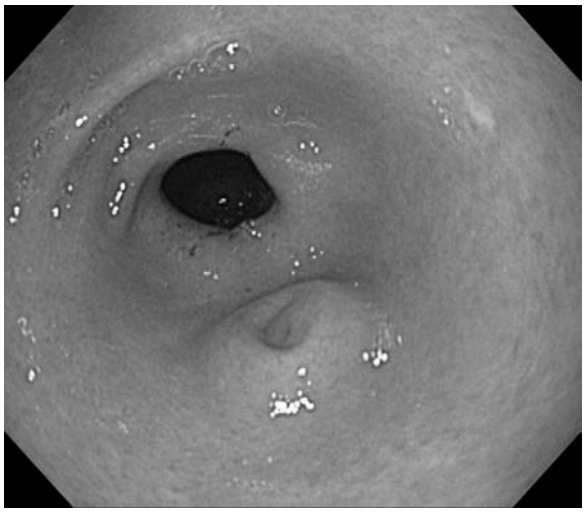

FIGURE 1. Heterotopic pancreas in the antrum of a patient with esophageal atresia.

had VACTERL syndrome (an association of at least 3 of the following malformations: vertebral, anorectal, cardiac, tracheal, esophageal, renal, and limb; Online Mendelian Inheritance in Man 192350), and among them, 5 (17%) had HP. There were no differences between the EA-TEF groups with or without HP for sex, prematurity, EA-TEF type, the presence or absence of esophageal stenosis requiring dilatation, VACTERL syndrome, or any other congenital abnormalities (Table 2).

DISCUSSION

This study demonstrates, for the first time, that gastric HP is clearly associated with EA-TEF, irrespective of other malformations. In the stomach, HP is most often located along the greater curvature of the prepyloric antrum.

Others have reported isolated cases of HP with EA. Pouessel et al (6) described 2 cases of gastric HP with EA-TEF. Yamagiwa et al (7) had 1 case of HP situated in the upper pouch of the atretic esophagus. Ozcan et al (8) reported 1 child with type C EA and esophageal HP that involved TEF, making the distal part of the esophagus atretic. According to these authors, the association was fortuitous. With 19% of HP in patients with EA-TEF, we definitively demonstrated a higher frequency compared with 0.5% in the control group. The presence of gastric HP in our control group (0.5%) is in concordance with that of HP in the general population after autopsies (1–2%) (4). Because HP can be multiple and localized not only in the upper gastrointestinal tract but also in the small bowel or in Meckel diverticulum (9), we cannot exclude that some patients with EA-TEF may have HP not located only in the gastroscopy-examined zones. However, it does not lead to underestimation of HP incidence in this population because a bias also occurs in the control group.

Other digestive malformations have been linked with HP. Ogata et al retrospectively investigated patients with HP who underwent laparotomy (9). They reported that 14.8% of patients with Meckel diverticulum, 5.6% of patients with malrotation, and 7.7% of patients with annular pancreas had HP. In the entire population of children with EA and/or TEF, the presence of associated malformation, either digestive or not, did not predict HP. In our population of patients with HP, only 1 child had a known malrotation, but no Meckel diverticulum or annular pancreas was found. However, because Meckel diverticulum has been more prevalent in patients with HP, we should pay more attention to this subgroup with EA-TEF and HP in our long-term follow-up.

HP treatment remains controversial. Usually, it is asymptomatic, and its management is observational, with surgery reserved for complicated cases (10). Complications can include ulceration, gastric outlet obstruction, intussusception, and pancreatitis. Malignant transformation is rare (11). For these reasons, some surgeons suggest that HP should be removed whenever it is encountered during laparotomy (9). For our patients with EA-TEF followed carefully since 2005, none had complications related to HP.

Our study has some limitations. We did not match case and control patients for age or sex because HP is thought to be a congenital malformation and should thus be present since birth. In this context, we do not feel that we underreported its prevalence in an older, general pediatric population attending a general gastroenterology clinic compared with patients with EA-TEF. Also, because endoscopy was reviewed retrospectively, there may be a recall bias that should be equal in both groups. Another limitation is that the final diagnosis is usually histological. During endoscopy, biopsies are often normal because HP is covered by a normal gastric epithelium. In this study, all of the endoscopies were performed by experienced endoscopists who reported macroscopically typical HP: a mass with central umbilication measuring about 2 mm to 4 cm. Moreover, 88% of HP were visually confirmed by pictures taken during the procedure.

TABLE 1. Demographics and incidence of heterotopic pancreas in patients with esophageal atresia with or without tracheo-esophageal fistula (EA-TEF) and controls

	EA-TEF (n = 91)	Controls (n = 182)
Age, y (mean, range)	7.7 (0.25–17.9)	10.2 (0.2–17.7)
Female sex, %	40 (44)	97 (53)
Presence of heterotopic pancreas (no., %)	17 (18.7)*	1 (0.5)

* OR 42, 95% confidence interval 7–249; $P < 0.001$.

TABLE 2. Characteristics of patients with esophageal atresia with or without tracheo-esophageal fistula according to the presence or absence of heterotopic pancreas

	EA-TEF with HP	EA-TEF without HP	P^*
Female sex, %	59	41	0.188
Gestational age <37 wk, %	25	43	0.26
EA-TEF type C†, %	94	79	0.286
VACTERL syndrome, %	29	31	1
Cardiac anomalies, %	35	52	0.281
Renal anomalies, %	29	18	0.314
Musculoskeletal anomalies, %	18	23	0.545
Digestive anomalies, %	24	19	0.748
Esophageal stenosis requiring dilatation, %	35	19	0.192

* Fisher exact test.
† Type C = EA with distal TEF.

Two theories of HP histogenesis have been proposed (12). One is its development from immigrated fetal pancreatic tissue, and the other is its occurrence from primitive gastric mucosal epithelium with subsequent erroneous differentiation into pancreatic tissue. Surprisingly, in the present study, we did not find a significantly higher incidence of duodenal (duodenal atresia) or pancreatic malformations (annular pancreas) in children with HP, which indicates that the latter hypothesis is more likely. The etiology and pathophysiology of EA-TEF are currently unknown. Whether the association between EA-TEF and HP may be related to the same developmental mechanisms remains to be investigated further and could lead to a new pathophysiological hypothesis of this poorly understood and debilitating condition.

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