Gastroesophageal reflux (GER) is one of the major sequelae in infants who survive congenital diaphragmatic hernia (CDH) repair. 1 – 3 The causal linkage between CDH and GER remains unclarified, whereas several possibilities have been addressed. 1,3,4 Stolar et al. have reported foregut dysmotility (esophageal ectasia, GER, delayed gastric emptying) to be a good example of a previously unrecognized consequence of CDH and an important source of morbidity in CDH survivors. 5,6 But reports concerning long-term gastrointestinal morbidity in patients with CDH are few and based on a small and heterogeneous number of patients. 7,8 The aim of the present study was to examine the gastrointestinal morbidity in infant, adolescent and adult patients who have undergone repair of CDH.

Methods

Between 1972 and 2002 64 patients with CDH were treated at the Department of Pediatric Surgery of University of Messina, Italy. The male : female ratio was 1:1.1 (male, n = 30; female, n = 34). In 56 patients the defect was on the left side and in eight patients it was on the right. In 53 neonates the hernia was diagnosed during the first 6–8 h of life, in 10 patients within the 24 h of life, in one the diagnosis was obtained when the child was 6 months old.

None of the patients had prenatal diagnosis. Surgical repair was performed through a subcostal or midline abdominal incision. Closure of the defect was achieved directly in 57 patients (89%). In seven cases (11%) a laparocele creation was also necessary. In seven patients (11%) diagnosed in the first 6–8 h of life a patch was necessary (three on the right, four on the left side).

In 31 patients (48.5%) the stomach was positioned in the thoracic cavity. Until 1985 the overall survival rate was 50% (13 surviving patients). Over the last 17 years, with the use of modern protocols, (extracorporeal membrane oxygenation therapy excluded) the overall survival rate was 80% (31 surviving patients). 9

Forty (91%) out of 44 survivors had a left diaphragmatic hernia and four (9%) a right diaphragmatic hernia. Thirty-one (81.5%) of 40 survivors of left diaphragmatic hernia repair were followed up.
The followed-up patients were subdivided into two groups: group A, 12 patients (38%; five male, seven female) with a mean age of 4.5 ± 1.8 years (range, 2–7 years), were operated on in the period 1997–2002. Group B consisted of 19 patients (61%; nine male, 10 female), with a mean age of 21.0 ± 5.7 years (range, 8–33 years), and they were operated on from 1972 to 1996.

The two groups were divided according to a previous criterion adopted in the same patients followed up for respiratory problems. To achieve a homogeneous and numerically sufficient number, we included in the study only patients with a left diaphragmatic hernia repaired without the use of a patch. The study was previously approved by the University of Messina Hospital Ethics Committee. During the follow-up visit a detailed medical history was obtained from the patient or parents. Symptoms suggestive of GER were classified according to Galmiche and des Varannes.

In addition, after informed consent, all patients underwent barium meal study and gastroesophageal scintigraphy. Only 26 patients (83.8%) accepted esophageal pH monitoring for 24 h and manometry of the esophagus and stomach. Upper intestinal endoscopy was performed only in patients with confirmed GER.

Upper gastrointestinal (GI) series with barium was performed according to the protocol standardized by McCauley et al. The position of the stomach, occurrence of GER and signs of esophageal ectasia and/or signs of esophagitis were reviewed. Standard criteria were applied.

Gastroesophageal scintigraphy was conducted using a solid standard meal of hamburger, mashed potato, and 200 mL milk with 15 g sugar. The mashed potato was mixed with 3.7 MBq technetium-99m sulfur colloid. The volume of the meal was 400 mL with an energy content of 2512 kJ and a pH of 6.2. The composition was 24 g protein, 70 g carbohydrate and 24 g fat. The examination was carried out in the early afternoon, 6 h after a light breakfast. Soon after the test meal the patient was laid on a bed with the collimator positioned on their stomach on the area of maximum activity. It was left in this position for 60–90 min. Time between meal ingestion and the initial recording was always 5–10 min. Registration of activity was recorded with dynamic image acquisition (one frame every 60 s) for 90 min. The acquisition was made using a wide field gamma camera fitted with a low-energy all-purpose collimator in anterior projection (Elscint-Apex 409 ECT, Haifa, Israel).

Ninety minutes was considered to be the upper limit for time taken for the stomach to empty half of its radioactive content (T½), according to previous experience. The residual fraction is the quantity of activity recorded in the stomach at the end of the study (90 min).

The esophageal pH monitoring was performed with a flexible glass electrode and an external electrode for reference. Data were collected and successively processed using a software package pH informer (Medical Instrument, Solothurn, Switzerland). The presence or absence of GER was evaluated using standard criteria. Manometry was carried out using a 2.2 mm probe with three solid state transducers each at 2.5 cm connected to a portable computerized recording unit. Data were collected and successively processed on a PC using SME Scan 4.3 (SME, Solothurn, Switzerland) dedicated software for recording and elaboration of the data. Patients fasted for at least 3 h. The interdigestive phases and the digestive motor activity of the stomach were evaluated during the ingestion of a liquid or solid bolus. At the end, a pull-through is performed to study the lower esophageal sphincter (LES), the esophageal body, and upper esophageal sphincter (UES). Three phases can be recognized in the interdigestive cycle (fasting phase): phase I, motor quiescence; phase II, irregular motor activity; and phase III, burst of coordinated contraction. I, II, and III waves alternate regularly during the three phases. An entire cycle lasts 90–120 min.

Data were compared with historic controls of the Institute of Nuclear Medicine for scintigraphy and of the Unit of Pediatric Surgery (Romeo G. et al., unpubl. data, 1982) for manometry. The results are expressed as medians and range. Non-parametric statistics (Mann–Whitney U-test) were used for the statistical analysis in the scintigraphy.

An upper intestinal endoscopy was performed with pediatric esophagus–gastro-fiberscope (Karl Storz, Tuttingen, Germany). Esophagitis was classified according to standard criteria. The Ismail-Beigi et al. histologic classification of inflammation was applied to biopsy specimens taken during endoscopy.

Statistical analysis

Fisher’s exact test was applied to compare group A and group B unless otherwise specified. P < 0.05 was considered significant.

Results

Clinical

At follow up all patients considered themselves or were considered by their parents to be fully healthy. All patients had a normal lifestyle. The growth of patients was normal; all of them were attending school with good results, three patients were graduates, one man was in competitive sport, and another one was a saxophone player. Three women had multiple uneventful pregnancies and one of these underwent cesarean section. Regarding digestive symptoms 20 of 31 patients followed (64%) had no major clinical concerns suggesting GER at the time of the follow-up study, but eight of them (41.7% of group A and 15.8% of group B) had typical symptoms in their history (P = 0.20; Fig. 1). Three patients were treated early for GER with Nissen fundoplication (10%).

Intestinal obstruction requiring surgical treatment occurred in four of the 31 patients survivors (13%), 3 months to 6 years after repair of the diaphragmatic defect.

Barium meal

Barium meal study was pathologic in 33.3% of patients in group A and 21% in group B (P = 0.675; Table 1). Particularly in three patients (10%) the study highlighted an esophageal dilatation. In six patients (19%) an hiatal hernia was evident (25% of group A, 18% of group B). GER was documented in eight patients (26%; 33% of group A, 21% of group B; grade 1, n = 2, grade 2, n = 5, grade 3, n = 1). Of five patients with hiatal hernia one had grade 1

© 2008 Japan Pediatric Society
and another two a grade 2 GER. In six patients (19%) a malposition of the stomach was present and in five of these cases GER was also present (83%). The size of the defect and the eventual use of laparoscopy had no statistically significant correlation with GER.

Six patients with GER at follow up had the stomach herniated in the thoracic cavity at the time of hernia reduction (75%). Differences between group A and B are summarized in Table 1.

**Scintigraphy**

Median gastric emptying was of 87.8 min (range 36–180 min) in the test group (Table 1), whereas the control group had a median of 64.5 min (40–75 min; \( P = 0.001 \)). In 14 patients (41.7% of group A and 47% of group B) the T½ to empty the stomach of the radioactive material was clearly pathologic over the upper limit of 90 min. The retention value was also higher compared with the control group (68% vs 39%, \( P = 0.008 \)). In 15 cases (48.3%; 58% of group A, 42% of group B) GER was documented (seven of group A, eight of group B; \( P = 0.472 \); eight of these were symptomatic and GER had already been diagnosed by barium meal). Twelve out of 13 patients (92%) had delayed gastric emptying. Eight out of 14 patients (58%) with pathologic T½ to empty the stomach had typical symptoms of GER in their history and 10 out of 15 patients (66.6%) with scintigraphic GER presented an intrathoracic stomach at the time of hernia repair. In the three patients with early fundoplication no evidence of reflux was observed and gastric emptying study was within the normal range.

**pH monitoring and manometry**

In 26 patients (group A, \( n = 11 \); group B, \( n = 15 \)) studied with 24 h pH monitoring (Table 2) a pathologic reflux in 11 (42.3%) was documented. Of these patients eight (80%) had typical symptoms of GER in their history. Particularly in group A, pathologic GER was documented in 54.5% of patients whereas in group B it was present in 33.3% of patients (\( P = 0.426 \)). In the other cases, including patients with early fundoplication, the examination was within the normal range.

Manometry demonstrated a normal basal pressure of the UES with normal post-deglutition relaxation; in the mid-esophagus the presence of bi-phasic waves were always recorded in nine patients (34.6%; five group A, 45.4%; four group B, 26.7%; \( P = 0.418 \)); the basal tone of the LES was in 60% of patients below the normal range (33–40 hPa) but with a normal and coordinated relaxation. Basal gastric pressure in all patients was positive (25–40 hPa) and within the normal range. In 15 patients (57.6%; seven group A, 63.6%; eight group, B 53.3%) the three fasting phases were represented regularly with normal duration of the third phase (antral clearing, 4–5 min) and normal peristaltic waves of type I, II and III in both frequency (>3) and amplitude. In particular, the peristaltic type III waves in the third phase presented with spikes of normal amplitude (>65–70 hPa). In 11 patients (42.4%; 36.4% group A, 46.7% group B; \( P = 0.70 \)), alterations were recorded. These involved mainly the duration of the third phase and the frequency and amplitude of the peristaltic waves. Antral hypomotility was caused by the increased duration of the third fasting phase and by a reduced amplitude of the type III peristaltic waves (<65–70 hPa). Eight patients with symptomatic GER and delayed gastric emptying at scintigraphy had also disturbed gastric activity at manometry. Another three patients with delayed gastric emptying presented at manometry with alterations in peristaltic activity but without any symptoms. One patient with hiatal hernia had altered manometry but without major symptoms or scintigraphic anomalies.

**Endoscopy**

Endoscopy showed macroscopic esophageal pathology in four (33%) of the patients with GER. Two patients had grade 1 esophagitis, two had grade 2 esophagitis. Of the two patients with grade 1 esophagitis one was 2 years old and the other was 6 years old. One patient with grade 2 esophagitis was a symptomatic adult, 33 years of age.

In addition, a hiatal hernia (2–7 cm) was present in six (54.5%) of patients with GER (two group A, four group B). Histology was pathological in seven (63.6%) of the 11 patients. Grade 1 histological esophagitis was found in four group A patients and one group B patient, and grade 2 in two group B patients.

Histological evidence of gastritis was found in four patients (36.3%; group A, \( n = 1 \); group B, \( n = 3 \)). The rapid urease assay for *Helicobacter pylori* was positive in all these patients.

<table>
<thead>
<tr>
<th>Group</th>
<th>Age(years)</th>
<th>T½ (%)</th>
<th>GER Scintigraphy (%)</th>
<th>GER Radiological (%)</th>
<th>Stomach position (intrathoracic)(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>A (( n = 12 ))</td>
<td>4.4 ± 0.5</td>
<td>80.9 ± 5.6</td>
<td>58</td>
<td>33</td>
<td>50</td>
</tr>
<tr>
<td>B (( n = 19 ))</td>
<td>21 ± 5.7</td>
<td>95.6 ± 5.7</td>
<td>42</td>
<td>21</td>
<td>36.8</td>
</tr>
</tbody>
</table>

\( P; \) NS; Fisher’s exact test for group A vs group B. CDH, congenital diaphragmatic hernia; GER, gastroesophageal reflux.

© 2008 Japan Pediatric Society
Helicobacter pylori was also present in the biopsy specimen of three patients from group B. Histological duodenitis was present in two patients (18%; group B); all of these also had histological evidence of gastritis.

Discussion

Postoperative symptoms suggestive of GER have occurred frequently in CDH survivors. During the first year of life, GER has been verified in 20–84% of patients with CDH,

In the present series, symptomatic early postoperative GER occurred in 35% of cases. But the nutritional problems tend to improve with age.

Even if the weight of the survivors with significant esophageal reflux was significantly lower than whose without at 1 year, by 2 years of age there was no significant difference.

This implies that early GER does not have a significant influence on physical development of those patients, as also demonstrated in the present study, in which survivors of CDH repair had no significant growth impairment.

Stolar et al. reported that GER in CDH patients did not require anti-reflux surgery and there was spontaneous amelioration as the patients grew and spent more time upright. In the authors’ experience a pathological GER was documented in 54.5% of the patients at mid-term follow up (group A); in the long term (group B) a pathological GER was present in 33.3% of patients. There was no statistical difference in the incidence of GER between the two groups.

In the present series 63.6% of patients with gastric endoscopy had histological esophageal pathology. The present results are in accordance with those of Vanamo et al., who found esophagitis in 54% of patients when performing follow-up endoscopy an average of 30 years after repair of CDH or eventration.

Histologically confirmed gastritis was present in 36.3% of patients with GER. In all cases, the gastritis was associated with H. pylori infection of the gastric mucosa. The prevalence of H. pylori infection did not differ from that among the general Finnish population with a similar age distribution.

The mechanisms responsible for pathologic GER have not been well clarified in survivors of CDH. Foregut dysmotility, reported by Stolar, is a good example of a previously unrecognized consequence of CDH and has become an important source of morbidity in CDH survivors.

The concept of foregut dysmotility, particularly in left-side hernias, may be related to the translocation of the stomach into the chest with kinking and obstruction of the gastroesophageal junction.

As Stolar et al. suggest, the mediastinal shift and compression associated with CDH may disturb the normal development and mobility of the intrathoracic esophagus, leading to chronic ectasia and impairement of LES function.

Additionally, relative esophageal obstruction due to kinking at the gastroesophageal (GE) junction may be the basis for in utero polydramnios and this may contribute to development of esophageal ectasia, in the same way as any other foregut atresia would. The formation of the gastroesophageal junction may be abnormal, especially if a significant portion of the stomach is herniated into the chest during organogenesis.

The Kieffer et al. data suggest that the presence of an intrathoracic stomach at the time of reduction is associated with pathologic GER. A shortened intra-abdominal esophagus and an obtuse angle of His have been implicated.

The present study found a significant relationship between GER and thoracic position of the stomach (42%). Frequent non-rotation of the stomach and the midgut may account for the malpositioning of the stomach, which was often football-shaped and vertically oriented.

The functional consequences can be demonstrated by upper gastrointestinal series that will show the abnormal-shaped stomach and delayed gastric emptying. GER may also be observed at the same time. Moreover, a study has demonstrated a significant delayed gastric emptying at scintigraphy that could be a cofactor in GER appearance.

In the authors’ experience, virtually every infant with CDH has some degree of foregut dysmotility.

Manometry of esophageal motility showed abnormal contractility with poor peristaltic propagation both at mid- and long-term follow up. Manometry of gastric motility also showed that peristaltic activity was disturbed in approximately 39% of patients after CDH repair.

The main alterations were recorded at the level of the interdigestive phases, with type III waves characterized by reduced amplitude and delayed duration of the third phase, corresponding to antral hypomotility. There are no previous studies on gastric manometry in survivors of CDH repair. The present study confirms that gastric motility disorders in repaired CDH are still present even in adulthood. But they are not always responsible for symptoms.

Gastric manometry, however, assesses also the interdigestive phase and is useful for recognition of motility disorders in patients with dyspepsia. The present study has confirmed a previous observation in which GER was reported to be a manifestation of generalized foregut motility disorders; therefore, delayed gastric emptying can be an important factor for GER, and also can complicate the postoperative course after anti-reflux procedure.

The long-term consequences of foregut dysmotility remain to be seen. Because these children are at risk for all the consequences of foregut dysmotility, their conditions will need lifelong follow up.
Another associated gastrointestinal problem observed in the long-term management of patients with CDH is that of gastrointestinal obstruction. Compared with a rate of 2.2% in all infants after laparotomy during childhood,26 bowel obstruction rates as intestinal obstruction. Compared with a rate of 2.2% in all infants long-term management of patients with CDH is that of gastro-

References