Adequate timing of diagnostic tests for gastroesophageal reflux in children with esophageal atresia

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Abstract

Objective. Recent guidelines made recommendations for the management of gastroesophageal reflux in patients with esophageal atresia (EA). However, the timing for some diagnostic tests remained somehow unclear. This investigation studied the tests for gastroesophageal reflux in children aged one year old and children aged two or three.

Material and methods. Patients with EA who underwent Multichannel Intraluminal Impedance-pH monitoring (MII-pH) and endoscopy-histology were studied retrospectively. Patients aged one when the test was performed were the YO group and patients aged two or three years old formed the OL group. Substantially impaired MII-pH was defined as total number of reflux episodes >105 or >85 (depending on age), or reflux index >10%. Substantially impaired endoscopy was defined as erosive esophagitis or Barrett's esophagus. Substantially impaired histology was defined as moderate-severe esophagitis or Barrett's esophagus. Conventional parameters and substantially impaired values of the tests were compared.

Results. Twenty-four patients were studied. Twenty-three MII-pH were performed (12 in YO and 11 in OL): percentages of abnormal conventional parameters of MII-pH were not significantly different in both groups. Twenty endoscopies with biopsies were performed (7 in YO and 13 in OL): percentages of esophagitis were not significantly different. Interestingly, 26.9% of all the tests performed in YO were substantially impaired vs. 10.8% of all the tests in OL ($\chi^2 = 2.7$; $p = 0.1$).

Conclusion. Considering the percentage of alarming results of diagnostic tests in the YO group it would be advisable that patients with EA undergo MII-pH and endoscopy-histology at one year of age.

Key Words: Esophageal atresia; Gastroesophageal reflux; Endoscopy; Esophageal Multichannel intraluminal impedance; Esophageal pH monitoring; Pediatrics.

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Momento adecuado para las pruebas diagnósticas de reflujo esofágico en pacientes con atresia de esófago

Resumen

Objetivos. Recientemente se han publicado recomendaciones para el manejo del reflujo gastroesofágico en pacientes con atresia de esófago (AE). Sin embargo, el momento de realización de algunas pruebas no está completamente aclarado. Esta investigación evalúa las pruebas para reflujo gastroesofágico en niños de 1 año y niños de 2-3 años.

Material y métodos. Estudio retrospectivo de pacientes con AE sometidos a impedanciometría-phmetría (IMpH) y a endoscopia-histología. Los pacientes con 1 año en el momento de la prueba formaron el grupo MEN, y los pacientes con 2-3 años, el grupo MAY. Se consideró IMpH sustancialmente alterada aquella con un número total de reflujos >105 o >85 (según la edad), o un índice de reflujo >10%. La endoscopia se consideró sustancialmente alterada si presentaba esofagitis erosiva o esófago de Barrett. La histología se consideró sustancialmente alterada si presentaba esofagitis severa-moderada o esófago de Barrett. Se compararon los parámetros convencionales y los sustancialmente alterados.

Resultados. Se estudiaron 24 pacientes. Se realizaron 23 IMpH (12 en el grupo MEN y 11 en el MAY); los porcentajes de los parámetros convencionales patológicos no fueron estadísticamente diferentes en ambos grupos. Se realizaron 20 endoscopias (7 en el grupo MEN y 13 en el MAY); los porcentajes de esofagitis no fueron estadísticamente diferentes. El 26,9% de todas las pruebas en el grupo MEN resultaron sustancialmente alteradas, frente al 10,8% en el MAY ($\chi^2 = 2,7$; $p = 0,1$).

Conclusión. Teniendo en cuenta el porcentaje de resultados alarmantes en el grupo MEN, sería recomendable realizar una IMpH y una endoscopia con biopsias a los pacientes con AE a la edad de un año.

Palabras Clave: Atresia de esófago; Reflujo gastroesofágico; Endoscopia; Impedanciometría intraluminal esofágica; pHmetría esofágica; Pediatría.

INTRODUCTION

Gastroesophageal reflux (GER) is frequently related to esophageal atresia (EA)[1,2]. It is considered a chronic

condition which can cause complications in childhood and adulthood[3-5]. Although this relationship between GER and EA is well known, there were scarce recommendations for the follow-up of GER in children with EA until the last decade. Initially, the timing of diagnostic tests was variable and clinical assessment was carried through despite the low specificity of GER symptoms[6,7]. Some authors considered that children would outgrow GER after twelve or twenty-four months[6,8]. Therefore, some groups performed tests at the age of two or three[9,10]. Other groups carried out scheduled tests at predetermined ages which included, at least, one year old, three years old and several more afterwards[11,12]. Recently, two specific guidelines for the management of GER in children with EA have been published.

The European Society of Pediatric Gastroenterology Hepatology and Nutrition-North American Society of Pediatric Gastroenterology Hepatology and Nutrition (ESPGHAN-NASPGHAN) guideline recommended monitoring acid reflux and endoscopy with biopsies after stopping proton pump inhibitor (PPI) therapy, regardless of the absence of symptoms. This guideline stated that GER was still common in children with EA after two years of age and the proposed algorithm for asymptomatic patients indicated that PPI should be administered for one year[13].

The European Reference Network for Rare Inherited Congenital Anomalies (ERNICA) Consensus Conference endorsed the performance of endoscopy at the age of one and a 24-hour pH monitoring (pHm) or multichannel intraluminal impedance-pH monitoring (MII-pH) once the treatment with PPI was discontinued. However, a precise timing for the end of the treatment with PPI was not defined due to the absence of scientific evidence[14].

Additionally, the performance of endoscopies in young children requires general anesthesia or deep sedation and its effects in neurodevelopment have not been completely clarified[15,16].

Thus, in this investigation we evaluated the tests performed to study GER in EA in a group of children aged one and a group of children aged two or three. The aim was to study if abnormal results of diagnostic tests were more frequent and severe at an early age.

MATERIAL AND METHODS

A retrospective investigation was developed. Children with EA and distal tracheoesophageal fistula, who were followed up between January 2013 and August 2020 at our hospital, were studied. Patients who underwent endoscopy with biopsies and MII-pH were considered for the study. Exclusion criteria were: age at the moment of diagnostic tests (children younger than 12 months old or older than 48 months old when the tests were performed were not included); long-gap EA; EA types A, B, D or E (Gross' classification); and fundoplication surgery performed before the tests.

At our unit, as a standard, patients with EA were treated with PPI from the neonatal period until the age of one year, unless symptoms were present, in which case the treatment was extended. If patients were under treatment, PPI were discontinued one week before the performance of MMI-pH or endoscopy.

MII-pH tracings were manually-visually reviewed and analysed with specific software. The following MII-pH parameters were registered: reflux index (percentage of time with pH < 4), acid clearance time, total reflux episodes, acid reflux episodes (with a nadir pH < 4), non-acid reflux episodes (with a nadir pH ≥ 4), bolus clearance time (in the most distal channel), percentage of proximal reflux episodes (which reached the two proximal impedance electrodes) and mean impedance baseline. The following values of MII-pH parameters were considered abnormal, taking previous works into account: reflux index >5%; acid clearance time >114.4; total reflux episodes >71; acid reflux episodes >55; non-acid reflux episodes >34; bolus clearance time >32[17,18]. A MII-pH was considered substantially impaired (SI-MMI-pH) when a patient had a total number of reflux episodes >105 (for <2 years of age) or >85 (for >2 years of age); or a reflux index >10%[19,20].

Endoscopies were performed using a 9.2 mm diameter endoscope. Endoscopic findings were described following the Hetzel-Dent classification for esophagitis (grade 0: normal appearance; grade I: mucosal erythema, hyperemia or friability; grade II: superficial erosions that involve <10% of the distal esophagus; grade III: ulceration or superficial erosions that involve 10 to 50% of the distal esophagus; grade IV: deep ulceration anywhere in the esophagus or erosions that involve >50% of the distal esophagus)[21]. Endoscopic Barrett's esophagus was diagnosed when a segment of salmon-pink coloured mucosa ascended more than 1 cm above the Z-line (normal esophagogastric junction). An endoscopy was considered substantially impaired (SI-Endoscopy) if there was Barrett's esophagus or erosive esophagitis (Hetzel-Dent grade ≥ II).

Whenever an endoscopy was performed, three or four biopsies of distal esophageal mucosa were obtained (2-3 cm above the Z-line). Biopsies of proximal esophageal mucosa were also taken to study the extent of esophagitis or an eventual eosinophilic esophagitis. Samples were stained with hematoxylin-eosin and analysed by pathologists. Histological findings were classified as: no-esophagitis; mild esophagitis (basal membrane hyperplasia); moderate esophagitis (neutrophil infiltration); severe esophagitis (erosion/ulcer of the epithelium)[20,22]. Eosinophilic esophagitis was diagnosed when biopsies showed ≥15 eosinophils per high-power field. Barrett's esophagus was defined by the presence of columnar epithelium which replaced normal squamous epithelium. Histology was considered substantially impaired (SI-Histology) if Barrett's esophagus, moderate or severe esophagitis was found.

Table 1. Basal characteristics and symptoms of the patients*.

Variable	*Value*
Birth weight (grams)	2,740 (1,988-3,320)
Gestational age (weeks)	38 (36-40)
Female sex	11 (45.8%)
Associated congenital disorders	
- Anorectal malformation	2 (8.3%)
- Congenital heart disease	10 (41.7%)
- Hypospadias	1 (4.2%)
- Hydronephrosis	1 (4.2%)
- Cleft palate	1 (4.2%)
- Brachycephaly	1 (4.2%)
Thoracoscopy	8 (33.3%)
Number of esophageal dilatations after surgery	2 (0-4)
Symptoms	
- Regurgitation or vomiting	11 (45.8%)
- Dysphagia or food impaction	8 (33.3%)
- Failure to thrive	1 (4.2%)
- Pyrosis	0 (0%)
- Apneic spells	3 (12.5%)
- Barking cough	14 (58.3%)
- Recurrent pneumonia or bronchitis	1 (4.2%)
- Agitation or irritability	1 (0%)

**Continuous variables are described with median, P_{25} and P_{75}. Categorical variables are described with number of cases and percentage.*

Table 2. MII-pH results of the whole sample*.

Parameter	*Value*
Reflux index	4.6 (2.4-8)
Acid clearance time (seconds)	96 (66-122)
Number of total reflux episodes	56 (36-76)
Number of acid-reflux episodes	25 (15-42)
Number of non-acid-reflux episodes	27 (16-42)
Percentage of proximal reflux episodes	20 (9-29)
Bolus clearance time (seconds)	14 (12-21)
Mean impedance baseline	2,305 (1,564-2,653)

**Variables are described with median, P_{25} and P_{75}. MII-pH: Multichannel Intraluminal Impedance-pH monitoring.*

Clinical symptoms were obtained from medical records of the patients from the neonatal period to the date when each diagnostic test was performed.

Children aged one (≥12 months of age and <24 months of age) formed the younger than 2 group (YO); children aged 2 or 3 (≥24 months of age and <48 months of age) were the older than 2 group (OL).

Patients with abnormal parameters in each test were compared, as well as children with SI-MII-pH, SI-Endoscopy and SI-Histology. Comparisons were made with the χ^2 test and the Mann-Whitney U test. Sensitivity and specificity were calculated to assess the relationship between symptoms and results in the diagnostic tests. Pertinent 95% confidence intervals (CI) were calculated.

Statistical studies were performed using Statistical Package for Social Sciences 17.0 (SPSS, SPSS Inc., Chicago, IL, USA).

This investigation was conducted using retrospective data and allowed by the Review Board of our institution.

RESULTS

Twenty-four patients were included in the investigation. Two children were not operated on at our hospital but were followed up after surgical correction for EA and met the inclusion criteria. Thirteen cases (54.2%) had one or more associated congenital disorders. Twenty-two patients (91.6%) experienced some sort of symptoms during the follow-up (from the neonatal period to the moment of diagnostic tests). Usually, these symptoms were not persistent and changed or appeared after intervals without symptomatology (Table 1).

Nineteen patients underwent both endoscopy and MII-pH, four patients only underwent MII-pH and one patient just underwent endoscopy.

Results from the twenty-three patients who were evaluated using MII-pH are summarised in table 2.

Twelve patients were younger than two (YO), and eleven patients were older than two (OL) when the MII-pH was performed. Children with abnormal MII-pH parameters in group YO and in group OL were compared: no statistically significant differences were found (Table 3).

Twenty patients underwent endoscopy and esophageal biopsies. Findings are showed in table 4. Seven patients underwent endoscopy before they were two years old (YO) and 13 patients underwent endoscopy after 24 months of age (OL). Eleven patients were on PPI therapy until the week before endoscopy was performed. In nine cases the treatment was interrupted previously: three of them (42.9%) were from the YO group and six of them (46.2%) from the OL group (without differences between groups: $\chi^2 = 0.02$; $p = 0.887$).

One case presented Barrett's esophagus both in the endoscopic evaluation and in the histological study: gastric metaplasia was found, with no evidence of dysplasia. This patient was part of the YO group and was not on PPI therapy when diagnostic tests were performed (PPI were discontinued at 12 months of age). A patient with eosinophilic esophagitis was also from the YO group.

The existence of endoscopic esophagitis (Hetzel-Dent grade ≥I or Barrett's esophagus) was compared between both groups, without statistically significant differences. Histological esophagitis (including Barrett's esophagus and eosinophilic esophagitis) was also evaluated in YO and OL: there were no statistically significant differences either (Table 5).

Table 3. Patients with abnormal results of each parameter from MII-pH in YO and OL groups.

Parameter	*YO (n = 12)*	*OL (n = 11)*	*Test and p-value*
Birth weight (grams)†	2,605 (1,922-3,283)	2,715 (1,972.5-3,280)	M-W U = 56; p = 0.821
Gestational age (weeks)†	37 (36-39.75)	39 (35.75-40.25)	M-W U = 46.5; p = 0.381
Esophageal dilatations†	1.5 (0.25-2.75)	3 (1.5-4)	M-W U = 39.5; p = 0.180
Age at the moment of the MII-pH (months)†	18 (17-22)	34 (30-43)	–
Abnormal reflux index*	6 (50%)	5 (45.5%)	$\chi^2 = 0.05$; p = 0.827
Abnormal acid clearance time*	4 (33.3%)	2 (18.2%)	$\chi^2 = 0.68$; p = 0.409
Abnormal total number of reflux* episodes	5 (41.7%)	3 (27.3%)	$\chi^2 = 0.52$; p = 0.469
Abnormal number of acid reflux episodes*	2 (16.7%)	1 (9.1%)	$\chi^2 = 0.29$; p = 0.590
Abnormal number of non-acid reflux episodes*	5 (41.7%)	3 (27.3%)	$\chi^2 = 0.52$; p = 0.469
Abnormal bolus clearance time*	1 (8.3%)	1 (9.1%)	$\chi^2 = 0.004$; p = 0.949
SI-MMI-pH*	4 (33.3%)	2 (18.2%)	$\chi^2 = 0.68$; p = 0.408

*†Described with median, P_{25} and P_{75}; *Number of cases and percentage; MII-pH: Multichannel Intraluminal Impedance-pH monitoring; SI-MMI-pH: Substantially Impaired Multichannel Intraluminal Impedance-pH monitoring; M-W U: Mann-Whitney U test.*

Table 4. Endoscopic and histological findings of the sample.

Test	*Finding*	*Number of cases (%)*
Endoscopy	Grade 0	9 (45%)
	Grade I	10 (50%)
	Grade II	0 (0%)
	Grade III	0 (0%)
	Grade IV	0 (0%)
	Barrett's esophagus	1 (5%)
Histology	No esophagitis	2 (10%)
	Mild esophagitis	13 (65%)
	Moderate esophagitis	2 (10%)
	Severe esophagitis	1 (5%)
	Barrett's esophagus	1 (5%)
	Eosinophilic esophagitis	1 (5%)

Table 5. Patients with endoscopic esophagitis and histological esophagitis in YO and OL groups.

Finding	*YO (n = 7)*	*OL (n = 13)*	*Test and p-value)*
Birth weight (grams)†	2,740 (1,640-3,320)	2,690 (1,959-3,145)	M-W U = 42; p = 1
Gestational age (weeks)†	38 (33-40)	37.5 (36-40)	M-W U = 37; p = 0.711
Esophageal dilatations†	3 (1-4)	1.5 (0-2.75)	M-W U = 27; p = 0.227
Age at the moment of the endoscopy (months)†	22 (19-23)	35 (30-46)	–
Endoscopic esophagitis*	4 (57.1%)	7 (53.8%)	$\chi^2 = 0.2$ (p = 0.888)
SI-Endoscopy*	1 (14.3%)	0 (0%)	$\chi^2 = 1.96$ (p = 0.162)
Histological esophagitis*	7 (100%)	11 (84.6%)	$\chi^2 = 1.20$ (p = 0.274)
SI-Histology*	2 (28.6%)	2 (15.4%)	$\chi^2 = 0.50$ (p = 0.482)

*†Described with median, P_{25} and P_{75}; *Number of cases and percentage; SI-Endoscopy: Substantially Impaired Endoscopy; SI-Histology: Substantially Impaired Histology; M-W U: Mann-Whitney U test.*

A total of 63 tests were performed in the sample (23 MII-pH, 20 endoscopies and 20 esophageal biopsies). Seven out of twenty-six tests (26.9%) were substantially impaired in YO (95% CI: 11.6-47.8%). Four out of thirty-seven (10.8%) tests were substantially impaired in OL (95% CI: 3-25.4%). There were no statistically significant differences ($\chi^2 = 2.7$; p = 0.1).

In the consultation prior to the performance of MII-pH, 11 out of 23 patients were symptomatic (47.8%). Sensitivity and specificity were obtained to evaluate if being

symptomatic before MII-pH could predict abnormal results in any of the parameters of the test: sensitivity was 47.1% (95% CI: 20.4-73.7%) and specificity was 50% (95% CI: 2-98%).

In the consultation prior to the performance of endoscopy, 10 out of 20 patients were symptomatic (50%). Esophagitis in endoscopy and histology were considered as references to assess the accuracy of symptoms. Sensitivity was 45.5% (95% CI: 11.5-79.4%) and specificity was 44.4% (95% CI: 6.4-82.5%) for endoscopic esophagitis. Regarding histological esophagitis, sensitivity was 55.6% (95% CI: 29.8-81.3%) and specificity was 100 (95% CI: 75-100%).

DISCUSSION

According to various authors, a considerable number of patients with EA and GER are asymptomatic[8,23]. In the present study, the sensitivity of symptoms for the detection of abnormalities in MII-pH or endoscopy and histology was low. This could be interpreted claiming that tests are needed in EA patients with no apparent symptoms, which is in accordance with ESPGHAN-NASPGHAN and ERNICA recommendations[13,14]. However, diagnostic tests should be ideally performed when their results lead to changes in the management of patients. In our sample, the majority of children had slightly altered parameters in diagnostic tests for GER; this is common in EA and might not require prompt intervention. Therefore, it is arguable that these tests could be delayed. The aim of creating the "substantially impaired tests" category (SI-MII-pH, SI-Endoscopy and SI-Histology) was to find parameters which described severe and warning findings that could imply immediate changes in the management of these patients. SI-Endoscopy and SI-Histology were defined considering widespread classifications[20-22]. In order to establish SI-MII-pH, two parameters were considered: total number of reflux episodes and reflux index. An investigation by Pilic et al. showed the mean and standard deviation (SD) of retrograde bolus movements in a considerable sample of pediatric patients[19]. We obtained the reference for substantially impaired reflux episodes in each age group by calculating the *mean+2SD* in Pilic results. The reference for substantially impaired reflux index was determined following previous articles which defined significant or severe GER when the reflux index was >10%[20,24,25].

Although guidelines clarified the management of GER in EA patients, there were some key aspects that remained, to some point, ambiguous[13,14]. One of them was the age when pHm or MII-pH should be performed[14]. The results of this investigation showed no statistically significant differences between groups in the percentage of abnormal conventional MII-pH parameters, nor in alarming MII-pH parameters represented by SI-MII-pH. However, the percentage of patients with SI-MII-pH was considerably higher in the YO group than in the OL group (almost double). This notable difference and the absence of statistical significance might be explained by the small size of the sample. Additionally, a similar contrast was also found in the percentage of cases that had an abnormal number of total reflux episodes, acid-reflux episodes and non-acid reflux episodes.

Considering the results obtained in MII-pH tests, two possible recommendations were drawn. Firstly, the performance of MII-pH before two years of age would be justified attending to the relevant differences in SI-MII-pH mentioned before. Thirty-three percent of children aged one had an altered MII-pH test with at least one alarming parameter (IR or total number of reflux episodes). These patients require a precise diagnosis (including the severity of reflux and its nature- acid or non-acid-) which might lead to modifications in their treatment and management. Secondly, MII-pH offers advantages over simple pHm in the diagnosis of GER in EA because it detects acidic and non-acidic reflux. In our sample, there were more patients with abnormal values of non-acid reflux than patients with abnormal values of acid reflux and the number of non-acid reflux episodes was also slightly higher. These results are in accordance with previous works about EA[7,26,27]. Moreover, recent investigations outlined the importance of bile acids and non-acid reflux in the development of metaplasia and esophageal carcinogenesis[28,29].

Another aspect which was evaluated in this investigation was the possibility to delay endoscopies with esophageal biopsies until children are older than two. Again, no statistically significant differences were found between an early test (YO) or a delayed test (OL). Therefore, a preliminary superficial judgement could tilt the balance in favor of the postponement of diagnostic tests until patients are older. However, there were two remarkable results which changed the perspective and pointed towards the performance of tests when children are one year old. The percentage of SI-Histology was nearly twice higher in YO than in OL, in an analogous manner to SI-MII-pH. Furthermore, a case of Barrett's esophagus was found in a patient from the YO group. Barrett's esophagus is a consequence of severe or prolonged GER. Although intestinal Barrett's esophagus is the histological type which is characteristically associated to esophageal cancer, gastric metaplasia is also considered a risk for carcinogenesis[28]. Besides, gastric Barrett's esophagus was a precursor of intestinal metaplasia in several investigations in children[4,11]. Thus, it could be crucial to make a prompt diagnosis to schedule an accurate follow-up and therapy.

A total of 63 diagnostic tests were evaluated for this investigation: over 25% of all the diagnostic tests in YO were substantially impaired. Considering the 95% confidence interval, a non-negligible 11.6-47.8% of patients with EA would obtain an alarming (substantially impaired)

result in any of the GER diagnostic tests when they are performed before two years old. It would be reasonable to identify these findings promptly in order to provide an adequate treatment for these cases and avoid possible complications.

The main limitation of this investigacion is the size of the sample. This could explain the absence of statistically significant differences between groups, particularly in comparisons related to SI-MII-pH and SI-Histology. Besides, the retrospective character of the study was a handicap for the collection of standardized data from patients: biopsies for the study of Barrett's esophagus were not taken homogeneously in all cases and symptoms were not registered using validated questionnaires.

In conclusion, no statistical differences in parameters of MII-pH and endoscopy-histology were found between YO and OL groups. However, taking into consideration the percentage of alarming results in diagnostic tests for GER found at an early age, it might be advisable to perform endoscopy with biopsies and MII-pH in patients with EA at one year of age.

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