İNFANTLARDA VE ÇOCUKLARDA GASTROÖZEFAGİAL REFLÜ HASTALIĞININ GASTOÖZEFAGİAL REFLÜ SİNTİGRAFİSİ İLE DEĞERLENDİRİLMESİ

Gastroesophageal Reflux Disease Evaluation by Gastroesophageal Reflux Scintigraphy in Infants and in Children

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ÖZET

Amaç: Bölümümüze gastroözefagial reflü hastalığı şüphesiyle gastroözefagial reflü sintigrafisi (GERS) için refere edilmiş infantlarda ve çocuklarda gastroözefagial reflü varlığının yanı sıra ilk reflü zamanı, reflü episodu sayısı, reflü indeksi (RI), gastrik boşalma yüzdesi, ve gastrik boşalma yarı zamanını retrospektif olarak değerlendirmeyi amaçladık.

Gereç-Yöntemler: 2007-2019 Yılları arasında GERS çekilmiş infantların ve çocukların verileri tekrar değerlendirildi. Tüm hastalarin dinamik GERS görüntüleri öncelikle vizüel olarak değerlendirildi. Sonrasında özefagus, mide ve gastrointestinal sistem dışı alanlara çizilen belli alanların, alınan tüm görüntüler üzerine eklenmesi ile zaman-radyoaktivite değişim grafikleri oluşturuldu (Figür 1). Elde edilen veriler istatistiksel olarak değerlendirildi.

Bulgular: Toplam 208 çocuk hastanın %38.5'i reflü pozitif (80/208) olarak değerlendirildi. Hastalar reflü episodu sayısına göre sınıflandırıldılar. Reflü sınıfı ile gastrik boşalma yarı zamanı arasında pozitif korelasyon ($p<0.001$, $r= 0.274$) ve reflü sınıfı ile gastrik boşalma yüzdesi arasında negatif korelasyon ($p<0.001$, $r= -0.259$) bulundu. İlk reflü zamanları arasında veya RI'leri arasında gruplar arası farklılık saptanmadı ($p>0.05$).

Sonuç: Çalışmamızda her iki grupta da fazla sayıda reflüsü olan hastalarda gastrik boşalma yarı zamanının uzadığını ve gastrik boşalma yüzdesinin de azaldığını saptadık. Ancak, gruplar arası gastrik boşalma yarı zamanları veya gastrik boşalma yüzdeleri arası farklılık saptanmadı. Buna bağlı olarak, yaş gruplardan bağımsız olarak, GERS değerlendirmesi yapılırken vizüel değerlendirmenin yanı sıra gastrik boşalma yarı zamanının ve gastrik boşalma yüzdesinin kantifikasyonun tanıya katkıda bulunmayı sağlar.

Anahtar Kelimeler: Gaströzefageal Reflü Sintigrafisi; Gastroözefagial Reflü Hastalığı; Gastrik Boşalma

ABSTRACT

Aim: Our goal was to evaluate the gastric emptying time in either reflux positive and negative children; and also the first reflux time, the number of reflux episodes in scintigraphy, reflux index (RI), and gastric emptying half time for liquids in infants and in children who were referred to our department for gastroesophageal reflux scintigraphy (GERS) with suspicion of gastroesophageal reflux disease (GERD).

Material and Methods: Dynamic GERS images were first evaluated visually and then regions of interests (ROI) were drawn on esophagus, stomach and background. Time-activity curves were generated and obtained values were statistically evaluated.

Results: Among 208 patients 38.5 % of the patients were reflux positive (80/208). There was a positive correlation between degree of reflux and gastric emptying half-time ($p<0.001$, $r= 0.274$) and there was a negative correlation between the degree of reflux and the gastric emptying percentages ($p<0.001$, $r= -0.259$). There were no significant differences between first reflux time and the reflux grades of patients and also there were no significant differences between RI and reflux grades of patients ($p>0.05$).

Conclusion: Our results show, in all groups, patients with a high number of reflux episodes have longer gastric emptying half-time with lower gastric emptying percentages. However, between groups, no significant difference was found in terms of gastric emptying percentage or gastric emptying half-time. Consequently, independently of age groups, quantitative analysis of GERS should include both the visual analysis of the reflux and also the quantification of gastric emptying half time, gastric emptying percentage which may contribute diagnosis.

Keywords: Gastroesophageal Reflux Scintigraphy; Gastroesophageal Reflux Disease; Gastric Emptying

Introduction

Gastroesophageal reflux (GER) is the passage of gastric contents into the esophagus, which is usually physiological and common in childhood. However, gastroesophageal reflux disease (GERD) is less common which may cause serious symptoms and/or complications, warranting medical management and diagnostic evaluation.

The aetiology of GERD is usually multifactorial. Although the low pressure of lower esophageal sphincter (LES), the frequency of transient LES relaxation, deterioration of esophageal clearance and damage to the esophageal mucosal barrier play an essential role in the gastroesophageal reflux pathogenesis, the impairment of functional and defence mechanisms of esophagus also have an impact.

Clinically the symptoms may be either related with gastrointestinal system, or respiratory system. The diagnosis of GERD can rely on various tests such as 24-h esophageal pH monitoring (pHM), multichannel esophageal intraluminal impedance testing (MII), combined MII and pHM (MII-pHM), gastroesophageal reflux scintigraphy (GERS), upper gastrointestinal barium contrast radiography, esophagoscopy and biopsy, motility studies and ultrasonography. However, particularly for the pediatric population, these tests have advantages and limitations, and none of them can be considered as an ideal test (1,2). The main challenge in the diagnosis is to differentiate the physiological GER events from GERD. In children old enough to describe their symptoms reliably, the diagnosis of GERD can be made clinically and it is generally not necessary to perform diagnostic tests.

GERS is a simple, noninvasive test, which may allow evaluation and quantification of transit through and reflux into the esophagus (3), the aspiration, caused by abnormal esophageal contractions and the quantification of the rate of emptying of liquid meals from the stomach.

GERS is known as an efficient examination for assessing the severity of reflux particularly when quantified with its parameters (4). Furthermore, it is an additional diagnostic test for the diagnosis and follow-up of GER in infants and children, which allows quantification of gastric emptying and detection of reflux aspiration into the bronchial system.

However, the lack of performance methods standardization and also the lack of standardization of the image processing limits the widespread use of GERS (5–7). A recent review evaluating the diagnostic tests in children suspected of GERD, concluded that the drawback of diagnostic accuracy and draw attention to the urgent need of well-designed randomized controlled trials (8).

Gastric emptying has an important role in the aetiology of GERD if it is delayed (9). The major explanation in the relationship between gastric emptying and GER is concerning the gastric distention contributing abnormal motor function of the gastric fundus. It is estimated that approximately 50% of pediatric patients with symptomatic GERD present with delayed gastric emptying in the absence of mechanical obstruction (10,11). The relationship between GER and gastric emptying has been discussed before, however, owing to the exact role of upper sphincter in avoiding aspiration in children, this subject needs further evaluation (12). Regarding that and beside the relatively low in number of studies with GERS, we have retrospectively evaluated our department's pediatric patients suspected of GERD, which have been acquired between years 2007-2019. Our aim was to assess the first reflux time, the number of reflux episodes, the reflux index, and also the gastric emptying half time and gastric emptying percentage for liquids in reflux positive and negative patients in infants and also in children.

Materials and Methods

Between years 2007-2019, among 208 pediatric patients with suspected of GERD who underwent GERS were evaluated after the approval by the ethical committee of our hospital with file number 162019E-19. Patients with any other systemic disease or patients under medication were excluded. The patients were further divided into 2 age groups; Group A, patients less than 24 months old, and Group B patients greater

than 25 months old.

All the patients acquired GERS after fasting of 4 hours. Technetium-99m tin colloid (7 microCi/kg body weight or 0.74 megabecquerel/kg, minimum dosage 200 microCi and maximum dosage 400 microCi) was orally administered in a mixture of thick orange juice for patients older than 2 years or in milk or formula for patients younger than 2 years old (20 mL/kg body weight, maximum 200 mL). After drinking of 30 mL of radiolabeled test liquid, the patient was given the remaining unlabeled portion of orange juice or milk or formula to wash out the residual oropharyngeal and esophageal activity (13,14). Subsequently, patients lay in the supine position under the gamma camera for 30 min and were kept immobile with elastic straps on legs. In total a 30 minute dynamic imaging was acquired in the anterior projection in 15-s frames using a matrix size of 128 × 128 matrix with a large field-of-view gamma camera equipped with a low-energy all purpose collimator, Siemens E. cam (Siemens Medical Solutions, Siemens E.CAM/e.soft gamma camera, USA). The patients were not given sedatives as GER can be affected by these medications and the patients with motion artifact were interpreted only by visual assessment.

On dynamic images, a region of interest (ROI) was drawn on esophagus and stomach on the most intense radiotracer uptake frame and counts were obtained. Time activity curves were derived from the ROI drawn over the esophagus and stomach, and background was subtracted (Figure 1).

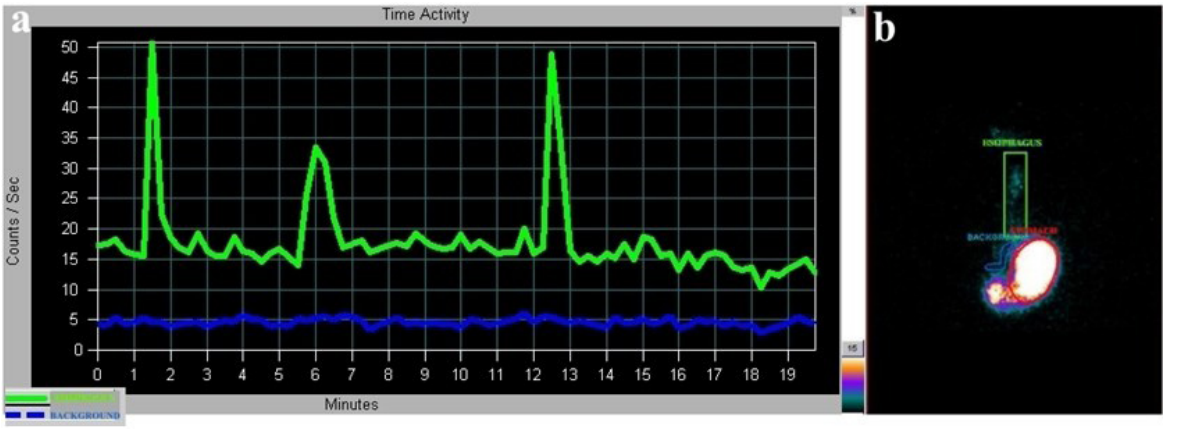

Figure 1. a) Time activity curves of b) Regions of interests (ROI) drawn over esophagus and background.

The retrograde activity in the esophagus displaying a 2-fold or more increment peak in the esophagus over the baseline in the time activity curve or the presence of radioactivity in the esophagus, more than 4% of the total gastric activity in any frame was accepted as a reflux episode. A reflux index (RI) was calculated as RI = (esophagus activity at the time of reflux - basal esophagus activity /stomach activity) × 100 formula.

According to the number of reflux episodes, a grading score based on the Blumhagen grading system and were as follows (15): Grade 0: no reflux; Grade 1: one or two episodes; Grade 2: three or four episodes; Grade 3: five or more episodes. An example of grade 3 reflux patient is presented in Figure 2.

Gastric emptying was defined as the time to reach half the peak counts and expressed as the quantitative half emptying time (t1/2). In a separate window new set of stomach and background ROIs were drawn and t1/2 and gastric emptying percentage are calculated from time activity curves (Figure 3).

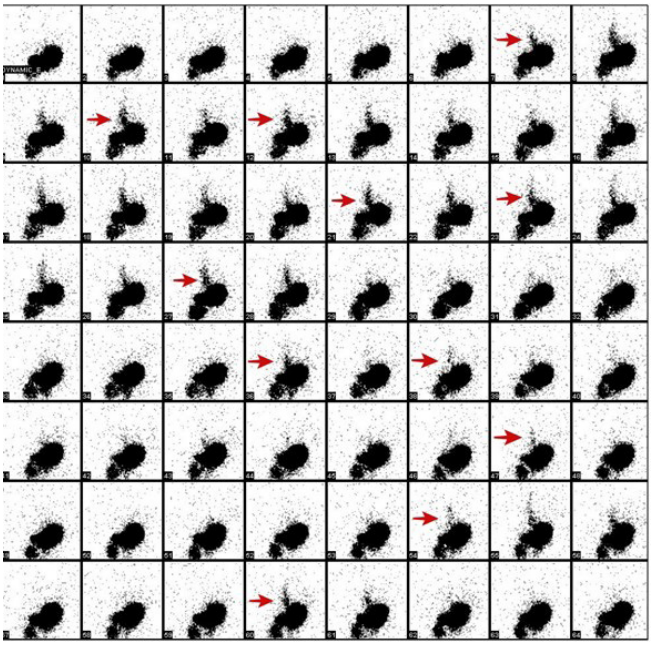

Figure 2. A grade 3 reflux positive 4-year-old male patient, in images at 15 seconds/frames. Reflux episodes are shown with red arrows.

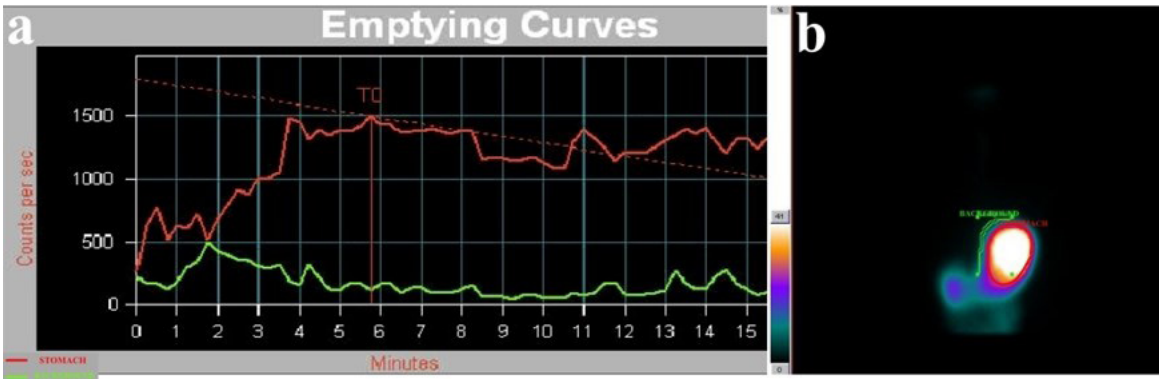

Figure 3. a) Gastric emptying curve derived from b) stomach and background ROI. Gastric emptying time is expressed as the half emptying time (t1/2) determined as the time it takes to reach half the peak counts and is calculated from the gastric emptying curve. T1/2 was 21 minutes for this case.

Statistical Analysis

Data analysis was performed using Statistical Package for Social Sciences for Windows software (SPSS version 23.0, SPSS Inc., Chicago, IL, USA). Kolmogorov-Smirnov test was used to examine whether the variables are normally distributed or not. The descriptive statistics are given as mean ± standard deviation for the numeric variables with normal distribution and for the numeric variables without normal distribution as median (minimum-maximum) values. To compare the numerical variables in groups, 2-tailed Student t tests for unpaired samples was used in case of normal distribution and Mann-Whitney U test was used in case of abnormal distribution. To compare groups more than 2, one-way ANOVA variance analysis was used. When the results of One-way analysis of variance and Kruskal-Wallis test showed a significant difference, the post-hoc Tukey HSD or Bonferroni multiple comparison test was used to determine the source of the difference. In all groups, the correlation between gastric emptying half time and gastric emptying percentage was done with Pearson correlation test. Values of $P<0.05$ were considered as statistically significant.

Results

Among 208 pediatric patients, there was 102 female (49.04%) and 106 male (50.96%) patients with a mean admission age was 38.18±30.8 months, age ranging from 3 months to 168 months. The duration of GER symptoms was 9.8±7.9 months (range: 1-48 months; median: 8.0 months). Chronic cough, nausea, regurgitation and vomiting were the most frequent symptoms. Among 208 patients, 128 patients (68 female and 60 male) were reflux negative with a mean age of 45.68 ± 32.9 months; and 80 patients (51 male and 29 female) were reflux positive with a mean age of 26.18 ± 22.7 months. Table 1 presented mean age, first reflux time, number of reflux episodes and RI of all patients according to their reflux grades.

The reflux positive patients were further graded into 3, according to number of reflux episodes. Thirty-six patients were graded as 1, 16 patients were graded as 2 and 28 patients were graded as 3 reflux positive.

Table 1. According to reflux grades the mean age, first reflux time, number of reflux episodes and reflux index (RI) of all patients are presented.

	Grade 0 (n=128)	Grade 1 (n=36)	Grade 2 (n=16)	Grade 3 (n=28)	p value
Mean age ± SD (months)	45.68±32.9	24.69±28.3	23.31±20.9	49.82±43.1	<0.05
First reflux time	-	466.67±248.1	562.5±179.2	503.57±325.1	>0.05
Number of reflux episodes	-	1.86±1.3	3.13±0.3	5.21±0.5	<0.01
RI	-	2.73± 0.6	3.25±0.7	4.10±1.0	>0.05

Table 2. The quantitative mean gastric emptying half-time (t1/2) and gastric emptying (GE) percentages of groups depending on their reflux grades are presented.

	In All Groups				Group A (0-24 month)				Group B (25-168 month)			
	Grade 0 (n=128)	Grade 1 (n=36)	Grade 2 (n=16)	Grade 3 (n=28)	Grade 0 (n=43)	Grade 1 (n=32)	Grade 2 (n=14)	Grade 3 (n=11)	Grade 0 (n=85)	Grade 1 (n=4)	Grade 2 (n=2)	Grade 3 (n=17)
GE t1/2	31.83± 13.1	33.90±11.4	31.81 ±6.9	44.07± 13.5	32.26± 11.5	33.59 ±11.6	30.36 ±5.9	48.27 ±16.6	31.61 ±13.8	36.25 ±11.2	42±5. 7	41.35 ±10.8
Significance	p=0.0001, f= 7.541				p= 0.011, x=11,124				p=0.039, f= 2.893			
GE percentage	26.99± 14.2	23.25±10.8	21.63 ±7.0	17.75± 5.4	24.49± 10.8	22.56 ±11.1	21.86 ±7.5	16.64 ±6	28.25 ±15.5	28.75 ±5.3	20±2. 8	18.47 ±4.9
Significance	p=0.002, x= 14.964				p= 0.039, x=8,185				p=0.02, x=9,891			

The patients were further divided according to 2 age groups; Group A, patients from 3 months to 24 months old; and Group B patients from 25 months to 168 months old. In Group A, there were 100 patients with a mean age: 14.9 ± 6.9 months and among 100 patients, 43 of them were reflux negative, and 57 of them were reflux positive. Among 57 reflux positive patients; 32 patients were graded as 1; 14 patients were graded as 2; 11 patients were graded as 3. In Group B, among 108 patients, 85 patients were reflux negative and 23 patients were reflux positive. Reflux positive patients were further graded into 3 and among 23 patients, 4 patients were grade 1; 2 patients were grade 2; 17 patients were grade 3.

By processing dynamic images the quantitative mean gastric emptying t1/2 and gastric emptying percentages of groups depending on their reflux grades are presented in Table 2.

TThe gastric emptying t1/2 was 31.83± 13.0 min in reflux negative patients whereas the gastric emptying t1/2 was 37.39± 12.5 min in reflux positive patients. However, the statistical differences between the reflux grades were significant (p=0.0001, f= 7,541). This difference is caused by the difference between the reflux negative group and the grade 3-reflux positive group (p<0.001). In Group A, the gastric emptying t1/2 was 32.26±11.5 min in reflux negative patients whereas the gastric emptying t1/2 was in reflux positive patients 35.6 ±13.1. In Group A, the statistical differences between the reflux grades were significant (p=0.011, x=11,124). This difference is caused by the difference between the reflux negative group and the grade 3-reflux positive group (p<0.05). In Group B, the gastric emptying t1/2 was 31.61± 13.8 min in reflux negative patients whereas the gastric emptying t1/2 was 40.52 ±10.4 min (p>0.05). However, the statistical differences between the reflux grades were significant (p=0.039, f= 2.893). This difference is caused by the difference between the reflux negative group and the grade 3-reflux positive group (p<0.05). The gastric emptying percentage was 26.99 ± 14.2 in reflux negative patients whereas the gastric emptying percentage was 21.0±8.7 in reflux positive patients. The statistical differences between the reflux grades were significant (P=0.002, x=14.964). This difference is caused by the difference between the reflux negative group and the grade 3-reflux positive group (p<0.05). In Group A, the gastric emptying percentage was 24.49 ±10.8 in reflux negative patients whereas the gastric emptying percentage was 21.3±9.6 in reflux positive patients (p>0.05). The statistical differences between the grades were significant (p=0.039, x=8,185). This difference is caused by the difference between the reflux negative group and the grade 3-reflux positive group (p<0.05). In Group B, the gastric emptying percentage was 28.25 ±15.5 in reflux negative patients whereas the gastric emptying percentage was 20.39 ±6.1 in reflux positive patients (p>0.05). However, the statistical differences between the grades were significant (p=0.02, x=9,891). We found that this difference is caused by the difference between the reflux negative group and the grade 3-reflux positive group (p<0.005).

When the two groups were compared, we found no significant difference between gastric emptying t1/2 or no significant difference between gastric emptying percentages (p>0.05).

Moreover, there were no significant differences between the first reflux time and the reflux grades of patients (p>0.05). And also we found no significant difference between RI and reflux grades of patients (p>0.05).

Furthermore, there was a positive correlation between patients with degree of reflux and the gastric emptying half-time (p<0.001, r= 0.274) and there was a negative correlation between patients with degree of reflux and the gastric emptying percentages (p<0.001, r= -0.259).

Discussion

The diagnosis of GERD is challenging because of the differentiation of physiological GER form GERD. Though severe reflux symptoms may be present by the age of 2 months, usually it has a benign course with a self-limiting condition, which improves with advancing gestational age, and about 60% of these patients are free of symptoms by the age of 18 months (7). However, about 30% of these patients have persistent symptoms till they are 4 years old and 5% of them

develop esophageal strictures, and another 5% die if they do not have adequate treatment (7). Furthermore, aspiration of gastric contents have been considered as a contributory cause of many sudden infant deaths (16). Therefore, the diagnosis is essential particularly in persistent and complicated cases.

In our study 38.5 % of patients were reflux positive (80/208) and 13.5 % of the total patients (28/208) and 35 % of reflux positive patients (28/80) were graded as 3. In Group A, 57 % of patients were reflux positive (57/100) and 11 % of this group (11/100) and 19.3 % of reflux positive patients (11/57) were graded as 3. In Group B, 21.3 % of patients (23/108) were reflux positive and 15.7 % of this group (17/108) and 73.9 % of reflux positive patients (17/23) were graded as 3. Consistent with the literature (17) reflux positive patients were common in Group A (57 %) compared to Group B (21.3 %). In Group A, 19.2% of reflux positive patients were graded as grade 3, however in Group B 73.9 % of reflux positive patients were graded as grade 3. We think that this difference may be because of selection of patients in different age groups. Such as mean age of Group A was 14.9±6.9 months consisting of patients who can not explain the symptoms properly whereas the mean age of Group B was 64.64±31.6 months involving patients who already have language skills. Furthermore, in reflux positive children over 3 years old require more chronic medical treatment compared to the majority of reflux positive children of whom their symptoms are resolved by the age of 2 without any longer need for treatment (18) may explain the elevated percentage of grade 3 patients in Group B compared to Group A.

The sensitivity of GERS for GERD has been reported to be between 75 % (19) to 100 % (20,21) whereas the specificity of GERS is around 100 % (19) but depends on the protocol used (22,23) and also the experience of the expert (20,21). However, because of the relatively low sensitivity reported in later reports (2), GERS may be indicated when GERD symptoms are not responding to standard therapies and other diagnoses or triggers such as delays in gastric emptying (2,24).

Gastric scintigraphy is the standard technique for the assessment of gastric emptying and the routine gastric emptying scintigraphy, can be acquired with either solids or liquids. However, apart from showing reflux in the esophagus, GERS may allow evaluation for both gastroesophageal reflux and gastric emptying at the same scan. The calculation of gastric emptying rate is an important factor in assessing reflux disease in children (23,25) which may contribute the diagnosis as the delayed gastric emptying may be a risk factor for GERD.

In our study we found that, the gastric emptying t1/2 is significantly greater and gastric emptying percentages are significantly lower in patients particularly with grade 3 reflux. Similarly, according to age groups, both groups' gastric emptying t1/2 were significantly greater in patients with grade 3 reflux. Likewise, the positive correlation between patients with degree of reflux and the gastric emptying half-time ($p<0.001$, $r=0.274$) and the negative correlation between patients with degree of reflux and the gastric emptying percentages ($p<0.001$, $r=-0.259$). Through the literature some studies reported that there is no apparent association between gastric emptying and reflux (26–28). However, our results supported the results of showed that delayed gastric emptying and severity of reflux grades are correlated (23,25,29). Through the literature reflux and its relationship between gastric emptying have been discussed in several age groups. An age-related difference in gastric emptying has been discussed in a pediatric population over 2 years old (28). Yet, in our study there was no significant difference between age groups ($p>0.05$).

We recognize that this study has limitations. The absence of asymptomatic control children limits our ability to infer any clinical relevance but for ethical reasons, we did not obtain a control study group and we could not look for variability. However, a study with asymptomatic and symptomatic pre-term infants, found no difference in incidence of positive GERS and grade of reflux (30). Another study evaluated the variability and reproducibility of GERS in pediatric patients with reflux and without reflux and found that variability is low (25). On the other hand, one must keep in mind that negative results do not mean that the

patient does not have GERD, while one reflux episode may represent physiological postprandial reflux.

Another limitation is due to radiation protection; the study has not been planned as a prospective study evaluating both the GERS and the gastric emptying scintigraphy for liquids in all children. Furthermore, because of the retrospective nature of the study, it was impossible to include the complete clinical data of the patients. Although it was not an aim, the results of GERS were not compared with those of the gold standard methods in this field. Such comparison has already been discussed in the literature (31).

Our results show that in all groups, patients with the high number of reflux episodes have longer gastric emptying half-time with lower gastric emptying percentages. Consequently, independently of age groups, the scintigraphic analysis of GERS should include both the visual analysis of the reflux and also the calculation of RI and the quantification of gastric emptying half time, gastric emptying percentage, which may contribute to the diagnosis.

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