Original Article / Orijinal Araştırma

Prevalence of Gastroeusophageal Reflux Disease and Reflux-Related Symptoms in Infants; Development and Validation of a Novel Gastroesophageal Reflux Disease Questionnaire to Use for Turkish Infants (SM Reflux Questionnaire)

İnfantlarda Gastroözofageal Reflü Hastalığı ve Reflü ile ilişkili Semptomların Sıklığı: Türk Çocuklarında Kullanılmak Üzere Yeni Gastroözefageal Reflü Hastalığı Anket Formunun Hazırlanması (SM Reflü Anketi)

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ABSTRACT

Aim: We aimed to analyze the prevalence of gastroesophageal reflux disease (GERD) in Turkish infants. For this purpose; we checked to see whether a previous questionnaire form (QF) may be used or not. We aimed to develop and validate a new questionnaire.

Materials and Methods: The study consisted of 3 groups of primary caregivers of infants with GERD, healthy infants and infants living in Menderes district. Previous QF for refkux were modified and checked in terms of utility; however it was concluded that it is not proper for GERD diagnosis. A new QF was created and reliability, sensitivity, specificity and validity were assessed.

Results: Test-retest and inter-rater reliability of the new questionnaire was 0.77 and 0.75, respectively. Cronbach coefficient α for internal consistency was 0.78. Sensitivity and specificity (reflux score ≥ 5) was 88% and 94%, respectively. Construct validity was studied with pH study and significant (p=0.046) but weak (r=0.21) correlation was found. GERD prevalence was found to be 14%. Mean age of the infants with GERD was significantly younger than those without GERD (p=0.0001). Duration of breastfeeding and exclusively breastfeeding was significantly low in infants with GERD (p=0.04 and p=0.015, respectively).

Conclusion: We developed and validated a new GERD QF to be used for Turkish infants. This form may be used in outpatient clinics for the assessment of GERD. *The Journal of Pediatric Research 2014;1(4):189-98*

Key Words: Gastroesophageal reflux disease, infants, prevalence, questionnaire

ÖZET

Amaç: Bu çalışmada Türk infantlarda gastroözofagial reflü hastalığı (GERH) prevalansını araştırmayı amaçladık. Bu amaçla daha önce kullanılmış anket formlarının kullanılabilirliğini araştırdık. Eğer kullanılabilir değilse de Türk çocuklarında kullanmak için yeni bir anket formu geliştirmeyi amaçladık.

Gereç ve Yöntem: Bu çalışmaya, GERH tanısı alan infantların bakıcıları, sağlıklı çocuklar ve Menderes ilçesinde yaşayan çocuklar olmak üzere 3 grup hasta ve sağlıklı çocuk alındı. Daha önceki reflü anketleri modifiye edilerek kullanılabilirliği değerlendirildi. Ama yapılan ön çalışmada bu anket formlarının GERH için kullanılabilir olmadığına karar verildi. Daha sonra yeni bir anket formu oluşturuldu. Soru başlıkları belirlendikten sonra güvenilirliği, sensitivitesi, spesifisitesi ve kullanılabilirliği araştırıldı.

Bulgular: Yeni anket formunun tekrarlanabilirlik ve kullanıcılar arasındaki güvenilirliği sırasıyla 0,77 ve 0,75 bulundu. Soru başlıklarının tutarlılığı için yapılan cronbach katsayısı 0,78 idi. Reflü skorunun ≥ 5 olması durumunda sensitivite ve spesifisitesi sırasıyla %88 ve %94 bulundu. pHmetre ile güvenilirlik çalışmasında anlamlı ilişki vardı (p=0,046) ama zayıftı (r=0,21). GERH prevalansı bu anket formu ile %14 bulundu. GERH olan çocukların yaşı daha küçüktü (p=0,0001). GERH olan çocuklarda anne sütü ile beslenme süresi ve sadece anne sütü alma süresi daha düşüktü (sırasıyla p=0,04 ve p=0,015).

Sonuç: Bu çalışmada Türk çocuklarında kullanılmak üzere yeni bir GERH anket formu geliştirdik. Bu formun polikliniklerde GERH tanısı için kullanılabileceğini düşünmekteyiz. *The Journal of Pediatric Research 2014;1(4):189-98*

Anahtar Kelimeler: Gastroözofagial reflü hastalığı, infant, prevalans, anket formu

Introduction

According to clinical practice guidelines of North American Society for Pediatric Gastroenterology, Hepatology, and Nutrition, and the European Society for Pediatric Gastroenterology, Hepatology, and Nutrition; pediatric gastroesophageal reflux (GER) is defined as the passage of gastric contents into the esophagus with or without regurgitation and vomiting (1). It is a normal physiological process occurring several times per day in healthy infants, children and adults. Most episodes of GER in healthy individuals last <3 minutes, occur in the postprandial period, and cause few or no symptoms. It is defined as gastroesophageal reflux disease (GERD) when the reflux of gastric contents causes troublesome symptoms and/or complications (1). GER is a common reason for pediatric visits and referrals to pediatric gastroenterologists. Approximately 70% of healthy 4-month-old infants regurgitate more than once a day, and one fourth of these infants' parents take their babies to pediatricians (2). Previous data suggest that the prevalence of GER is age dependent with the highest prevalence in infants younger than 6 months of age (2,3). On the other hand, there is limited data about the true prevalence of GERD in infants and children. The lack of epidemiological studies on GERD is mainly related to the lack of a definite diagnostic approach in population-based studies because symptoms related to GER or GERD are non-specific such as crying, irritability and fussiness, making it difficult to distinguish between healthy and sick infants (1). Epidemiological studies in adults suggest that the nature of GER may be different among different ethnic groups (4). It was reported to be more common in Western countries than Eastern countries (5,6). In addition; recent studies in children have suggested that genetic factors may play a role in GERD, and thus it is claimed that its prevalence and severity might vary according to racial and ethnic background (7). The prevalence of GER (especially with regurgitation) in American infants was found to be 50% in 0 to 3-month-olds, 67% in those aged 4 to 6 months, 21% in 7 to 9-month-olds and 5% in infants of 10 to 12 months; whereas it was found lower in Thai infants (2,5). In most infants, the regurgitation has a benign prognosis with spontaneous resolution after 6-8 months. Only 1 of 210 infants developed GERD during a 24 month follow-up period in an Italian study (3). The prevalence of troublesome GERD ranging from mucosal changes to complications is reported to be 5-8% in infants. (8). Koda et al. found the prevalence of GERD to be 18.2% in infants admitted to the pediatric gastroenterology service with reflux-related symptoms (9). The percentage of pathological GER was 11.15 in infants younger than 1 year of age according to Rome II criteria in a university pediatric gastroenterology service (3). Although many questionnaire forms about the symptoms of GERD have been developed in order to assess the prevalence of GERD in adult population, infants and children have been studied less commonly.

Orenstein et al. reported on the Infant Gastroesophageal Reflux Questionnaire (I-GERQ) developed before 2000, and it was later translated into many European languages (10). It was also revised in order to evaluate the outcome of the treatment (11). However, predicting the severity of GERD in infants with questionnaires is still a major problem in questionnaire based studies.

In this population based study; we aimed to analyze the prevalence of GERD in Turkish infants (<24 months). For this purpose we analyzed previous questionnaire forms to see whether they may be used or not. In the case of their unsuitability we aimed to develop and validate a novel questionnaire.

Material and Methods

Study Population

The study population consisted of primary caregivers (group 1) of infants with GERD (n=45, mean age ± SD: 15.8±7.8 months, 51.1% female), and healthy infants (group 2) not under medical/dietary treatment, without any known chronic illness or concomitant disease that could produce symptoms like GERD (n=100, mean age ± SD: 15.2±7 months, 48% female), and infants living in the Menderes district of İzmir (group 3). All the infants were <24 months of age. Menderes is about 20 kilometers away from İzmir, the population is heterogeneous with low income because the residents are mostly emigrants from the east and south parts of Turkey. A study was also done on adults by a gastroenterologist in the same area in order to analyze the prevalence of GERD in adult population (12). The population of Menderes was 63,899 according to the last census in our country and the age of 4.178 inhabitants was under 6. A sample size of 199 infants (mean age ± SD: 14.3±8 months, 48.7% female) was, evaluated based on the 15% prevalence of GERD in early infancy from previous reports with 95% confidence and 3% standard deviation. The GERD population (group 1 consisted of patients clinically diagnosed by experienced pediatric gastroenterologists with symptomatic GERD as demonstrated by the presence of typical GERD symptoms with (n=23, 51.1%) or without confirmatory tests (including endoscopy, a 24-hour pH study, flexible fiberoptic laryngoscopy examination). Caregivers were required to live in the same household as the infant to be able to communicate and understand the language (without mental and psychiatric retardation). Demographic characteristics of the study population and caregivers are shown in Table 1.

Study Design

A modified infant reflux questionnaire was planned to use for the study (8). It was translated into Turkish using standard translation methodology. For cultural validation, a version was pilot-tested by expert Turkish linguists. For example, terms such as "coffee spoon" and "soup spoon" are not routinely used in daily Turkish, so "tea spoon" or "spoon" were used instead. A preliminary analysis was done in order to check

the suitability of the questionnaire. Items were evaluated by "Ege Reflux Group", a group of physicians in Ege University including adult gastroenterologists (specialists on esophagus diseases) (n=5), ear nose and throat specialists (n=2), general surgeons (specialists on esophagus surgery) (n=3), specialists of chest diseases (n=2), psychiatrists (n=2), pediatric gastroenterologists (n=4) and pediatric pulmonologists (n=3). The group was founded in 2002, and assembles every Wednesday. Each item in the questionnaire was discussed in detail for a period of 2 months. A revised questionnaire form was developed based on the items on the reflux questionnaire form by Salvatore et al. with some revisions (8). After an agreement was reached on the context of the questionnaire, items were completed by the subgroup of the caregivers of the infants in group 1 and group 2 in a face-to face interview. The results were discussed in the group again, and it was concluded that the discrimination of infants with GERD from healthy infants with this questionnaire form was difficult (AUROC=0.94, best cut-off value: 8, specificity

94, sensitivity 86.7, GERD prevalence was found 10% in a subgroup of infants in group 2 "infants known as healthy"). The major factor was cultural differences and the different symptomatology of Turkish infants with GERD. For example, most of the parents responded "no" to the item "does your child refuse feeding even when hungry?" because "irritability or fussiness such as crying and grimacing outside(?) feeding" is more understandable by parents. Respiratory symptoms and upper respiratory problems such as common cold and otitis were common in Turkish infants with GERD (13,14). In addition, responses to some of the items such as "does your child suffer from chronic diarrhea?" and "does your child have chronic constipation?" did not differ between children with and without GERD. Therefore, the group decided to develop a novel questionnaire for Turkish infants.

Selection of Symptoms

A questionnaire including two major items (demographic features and symptomatology) was designed to be completed by the caregivers of the infants. Major symptoms of GERD were

Table I. Baseline demographic characteristics of the study population and caregivers	Group 1 (n=45)	Group 2 (n=100)	Group 3 (n=199)
Infant characteristics			
Age in months, mean ± SD	15.8±7.8	15.2±7	14.3±8
Age distribution, n (%)			
≤6 months	10 (22.2)	12 (12)	47 (23.6)
>6-12 months	4 (8.9)	29 (29)	37 (18.6)
>12 months	21 (68.9)	59 (59)	115 (57.8)
Gender, female n (%)	23 (51.1)	48 (48)	97 (48.7)
Weight, kg ± SD	10±2.6	10.3±2.7	9.7±2.8
Height, cm ± SD	78.9±11	76.1±10.2	73.7±11.8
Birth weight, kg ± SD	2.9±0.8*[a]	3.2±0.6[b]	3.2±0.5[c]
Type of delivery, normal n (%)	12 (26.7)	33 (33)	87 (43.7)
Gestation week, <37 wk n (%)	7 (15.6)	10 (10)	11 (5.5)
In vitro fertilization, n (%)	2 (4.4)[d]	0[e]	0[f]
Duration of breastfeeding months, mean ± SD	9±6.5	10±5.9	9.2±6.8
Exclusive breastfeeding months, mean ± SD	4.6±2.2	5.1±2.4	4.9±2.8
Caregiver characteristics			
Mother of the infant, n (%)	40 (88.9)	87 (87)	174 (87.4)
Age of the mother, years mean ± SD	31.6±5.2[g]	29±4.6[h]	27.5±5.3[i]
High school or more, n (%)	32 (71.1)	60 (60)	42 (21.1)
Housewife, n (%)	30 (66.7)	66 (66)	172 (86.4)
Age of the father, years mean ± SD	34.4±5.2	33.3±5.3	31.4±5.4
High school or more, n (%)	34 (75.5)	64 (64)	56 (28.1)
Public servant, n (%)	13 (28.9)	29 (29)	5 (2.5)
Number of siblings, ± SD	0.7±0.7	0.5±0.6	0.7±0.8
Monthly income, TL, mean ± SD	2467.7±591.7[j]	1374.2±865.3[k]	756.2±361.9[m]
Passive smoker, n (%)	20 (44.4)	53 (53)	120 (60.3)
Physician diagnosed GERD in the parents, n (%)	12 (26.7)[n]	13 (13)[o]	26 (13.1)[r]
*p[a-b, a-c, d-e, d-f, g-h, g-i, j-m, k-m, n-o, n-r]<0.05			

derived from the literature. In addition, respiratory symptoms in infants related to GERD were discussed in the group. Demographic items (26 questions) and symptom items (17 questions) were added to the questionnaire. The symptom items were on vomiting, the type of vomiting, crying related to feeding, refusing feeding, cyanosis during or after feeding, arching back, symptoms outside, behavior of chewing or swallowing outside feeding, feeding habits before sleeping or at night, drooling, hiccups, cough related to feeding, frequency of lower respiratory tract infections (such as bronchitis or pneumonia), growling or wheezing, frequency of upper respiratory tract infections (common-cold, flu-like symptoms), hoarseness and failure to gain weight. The questionnaire was developed and validated by the analysis of responses for infants with GERD (group 1) and healthy controls (group 2). Then the questionnaire was applied to the infants in the Menderes region (group 3) in order to evaluate the prevalence of GERD in infants.

Statistical Analyses
Item Performance and Scoring Algorithm

Characteristics of individual questionnaire items were examined by calculating the mean, minimum and maximum responses (assessing the floor and ceiling effects), percentage of missing and item-total correlations. Chi square tests and calculation of odds ratios were used to determine whether responses to individual items on the questionnaire were significantly different between the healthy and GERD infants, and the odds of having GERD based on individual items. If queried symptoms appeared with very low frequency or had statistically similar prevalence and frequency in both infants with GERD and healthy controls, these symptoms were dropped from the questionnaire. A scoring system was used ranging from 0 to 3 according to odds ratios of sub-items between healthy and GERD infants.

Sensitivity and Specificity

A receiver operation curve (ROC) plots the sensitivity of a particular score as a cut point against its specificity, with the objective identifying a score that best differentiates between infants with and without GERD. ROCs were used to evaluate sensitivity and specificity of questionnaire scores.

Reliability

Test-retest reliability, with intraclass correlation coefficient (ICC), was evaluated via a telephone interview 2 weeks after the initial test in subgroup of infants in group 1 and 2 by the same physician (S.R). The inter-rater reliability was evaluated by asking questionnaire items to secondary caregivers (15 secondary caregivers in group 1, and 26 secondary caregivers in group 2). An ICC >0.70 demonstrates acceptability both in test-retest reliability and the inter-rater reliability (15). The interobserver reliability was not evaluated because all the questionnaires were performed by the same observer (S.R). Internal consistency reliability was estimated using Cronbach coefficient α, for which values >0.70 are generally accepted for aggregate data (15).

Validity

Content validity of the study was attained by the proposals of expert physicians in Ege Reflux Group during a 2-month period. Discriminant validity was assessed by comprehension of the reflux score of the infants with (group 1) and without (group 2) GERD by using t tests. Spearman correlation coefficients were used to assess the relationship between reflux score and distal probe reflux index in the 24 hour pH study in the subgroup of infants with GERD (n=17) in order to analyze the construct validity.

The ethics committee of the Faculty of Medicine, Ege University, approved this study. All parents were fully informed of the nature of the study and they gave written and verbal consent before participating.

Results

Item Selection and Analyses

Results from item descriptive statistics, item differentiation between infants with and without GERD and expert clinician review were used to produce the final questionnaire. One of the symptom items "feeding habit before sleeping or at night" was deleted due to lack of significant difference between the infants with and without GERD (77.8% vs. 84%, p=0.366). Then the other items were finalized (total 16 items), a variety of scoring algorithms were explored. The optimal scoring algorithm was developed to produce total scores that could be calculated quickly and interpreted easily. Higher scores represent greater symptom burden. Items are summed, yielding a total score ranging from 0 to 40 (Appendix 1).

Reliability

Intraclass correlation coefficient for test-retest reliability was evaluated by a telephone interview 2 weeks after the initial test in the subgroup of infants in groups 1 and 2, and inter-rater reliability was 0.77 and 0.75, respectively. Cronbach coefficient α for the internal consistency was 0.78, which shows good internal consistency.

Sensitivity and Specificity

Reflux scores (mean ± SD and range) according to the final questionnaire for infants with GERD and without were 10.1±4.7 (2-22) and 2.4±1.8 (0-10), respectively. The area under the receiver operation curve (AUROC) for the diagnosis of GERD was 0.96 (p<0.0001; 95% confidence interval, 0.93 to 0.99) (Figure 1). With a cutoff value of reflux score ≥5, the sensitivity and specificity was 88% and 94%, respectively.

Positive predictive (PPV) and negative predictive values (NPV) for the reflux score ≥5 were 86.9% and 94.9%, respectively. Thus; a total score of ≥5 was accepted as GERD in infants.

Validity

As mentioned above, reflux score was significantly different between the infants with and without GERD (10.1±4.7 vs. 2.4±1.8, p<0.0001), which shows the discriminant validity of the questionnaire. Correlation between the reflux score and the 24-hour pH study was evaluated in the subgroup of infants with GERD (n=17) for the construct validity. There was significant (p=0.046) but weak (r=0.21) correlation between reflux score and distal reflux index. Median time

to complete the questionnaire in healthy infants and infants with GERD was 15 minutes (range; 5-20 minutes) and 20 minutes (range; 5-30 minutes), respectively.

GERD Prevalence and Related Symptoms

Mean ± SD reflux score was 2.4±3 (range: 0-28) in infants living in the Menderes district of Izmir, and GERD prevalence was found to be 14% (n=28) (reflux score ≥5) (95% CI: 9.18-18.82%). Reflux score was 8.1±4.5 and 1.5±1.2 in infants with and without GERD, respectively (p<0.001). Mean age of the infants with GERD was significantly younger than those without GERD (8.9±7 months vs. 15.2±7.9, p=0.0001). It was more common in infants ≤6 months of age (31.9%, 95% CI: 18.5-45.2%) compared to both infants >6 - ≤12 months of age (10.8%, 95% CI: 0.8-20.8%) and > 12 months of age (7.8%, 95 CI: 2.9-12.7%) (p=0.04, OR: 3.87, 95% CI: 1.04-15.55 and p=0.0002, OR: 5.52, 95% CI: 2.3-15.2, respectively) (Figure 2). GERD prevalence was 10.3% and 17.6% in female and male infants, respectively (p=0.199). In addition; the duration of breastfeeding and the duration of exclusively breastfeeding was significantly low in infants with GERD (7±5.8 months vs. 9.6±6.9, p=0.04 and 3.8±2.3 vs. 5.1±2.9, p=0.015, respectively). The number of siblings and the parents' age did not make a significant difference between infants with and without GERD. Passive smoking was more common in the parents of infants with GERD compared to other infants (71.4% vs. 58.4%, p=0.275). Overall and subgroups (with and without GERD) symptoms prevalence of infants is shown in Table 2. The prevalence of vomiting was 14% and vomiting > 5times/day was 2%. Symptoms such as vomiting (especially 3-5 times/day), gagging, crying during or after feeding (especially 3-5 times/day), refusing feeding even when hungry (especially 3-5 times/day), chewing or swallowing outside(?) feeding, hiccups during or after feedings and coughing during or after feedings had the odds ratios >20 for predicting GERD in infants.

Discussion

The excessive increase in prescribing anti-reflux medications for the reflux related symptoms in infants necessitated the development of reliable and sensitive non-invasive diagnostic methods. Questionnaire-based diagnosis is a non-invasive and simple method but it has some drawbacks. For example, the infants could not express their symptoms, so; diagnosis was made based on the responses of the caregivers, which were mainly related to their observations and which in turn could cause over or underestimation of the infant's symptoms. Also there are many similarities between physiological and reflux related symptoms.

Reflux questionnaire was first developed by Orenstein SR et al in 1993, and it was later validated for clinical use in 1996 (10). The major problem with the questionnaire was the lack of items related to reflux associated respiratory problems such as chronic cough or upper and lower respiratory tract infections. Salvatore S et al. modified Orenstein's questionnaire in 2005, and analyzed the correlation between

the reflux score, pH study, and histology which revealed poor correlation between the symptoms and acid exposure measured by pH-metry and esophagitis as evaluated by histologic examination (8). Deal L et al. developed a novel questionnaire for infants and young children in order to analyze the frequency of GERD symptoms (16). They also aimed to measure the validity of the questionnaire for the analysis of the responses to therapeutic treatments. As in Orenstein's questionnaire, respiratory problems were not taken into account in Deal's questionnaire (16). Prevalence and symptomatology of GERD may be different among different populations. In previous studies and in our clinical practice, respiratory problems and GERD are nested together particularly in infants (13,14). We found that coughing after or during feeding, growling outside the flu-like symptoms and
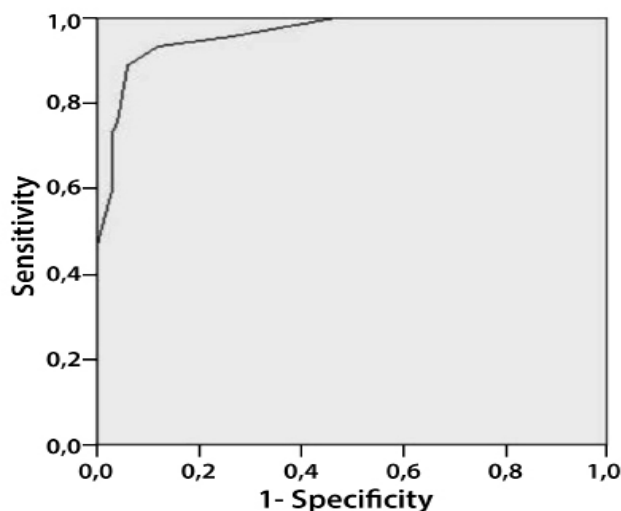
Figure 1. The receiver operation curve of novel questionnaire form (SM questionnaire) to examine its predictive use for assessing presence of GERD (area under the receiver operation curve (AUROC)=0.96, p<0.0001, 95% confidence interval: 0.93-0.99, best cut-off value ≥5, sensitivity: 0.88, specificity: 0.94, positive predictive value: 86.9% and negative predictive value: 94.9%)

Figure 2. Prevalence of gastroesophageal reflux disease (GERD) according to age groups. Red bar indicated the 95% confidence intervals

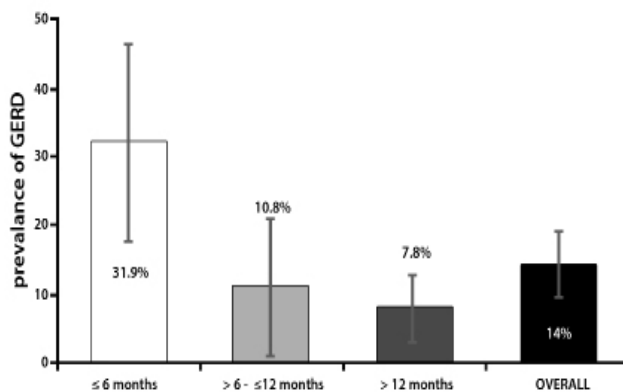| Table II. Reflux symptoms in infants in Menderes district					
Questions, n (%)	Overall (n=199)	Reflux Score < 5 (without GERD) (n=171)	Reflux Score ≥ 5 (with GERD) (n=28)	p	Odds Ratio
Q1: Vomiting	28 (14)	11 (6.4)	17 (60.7)		22.4
1-2 times/day	18 (9)	8 (4.7)	10 (35.7)		11.3
3-5 times/day	6 (3)	1 (0.6)	5 (17.8)	<0.0001	36.9
> 5 times/day	4 (2)	2 (1.1)	2 (7.1)		6.5
Q2: Type of vomiting					
Regurgitating	17 (8.5)	8 (4.7)	9 (32.1)		9.6
Belching	9 (4.5)	3 (1.7)	6 (21.4)	<0.0001	15.7
Gagging	5 (2.5)	1 (0.6)	4 (14.2)		28.3
Q3: Crying during or after feeding	15 (7.5)	6 (3.5)	9 (32.1)	<0.0001	13
≥6 times/day	1 (0.5)	0	1 (3.6)		-
3-5 times/day	4 (2)	1 (0.6)	3 (10.7)	0.009	20.4
<3 times/day	10 (5)	5 (2.9)	5 (17.8)	0.005	7.2
Q4: Refuse feedings even hungry	29 (14.5)	15 (8.7)	14 (50)	<0.0001	10.4
≥6 times/day	1 (0.5)	0	1 (3.6)		-
3-5 times/day	9 (4.5)	2 (1.1)	7 (25)	<0.0001	28.1
<3 times/day	19 (9.5)	13 (7.6)	6 (21.4)	0.03	3.3
Q5: Having cyanosis during or after feeding	2 (1)	1 (0.6)	1 (3.6)	0.142	6.3
Q6: Arching back during or after feeding	69 (34.6)	46 (26.9)	23 (82.1)	<0.0001	12.5
Q7: Irritability or fussiness outside the feeding	34 (17)	18 (10.5)	16 (57.1)	<0.0001	11.3
≥6 times/day	1 (0.5)	0	1 (3.6)		-
3-5 times/day	7 (3.5)	2 (1.1)	5 (17.8)	0.0006	18.3
<3 times/day	26 (13)	16 (9.4)	10 (35.7)	0.0007	5.3
Q8: Chewing or swallowing outside the feeding	7 (3.5)	1 (0.6)	6 (21.4)	<0.0001	46.3
≥6 times/day	0	0	0		-
3-5 times/day	2 (1)	0	2 (7.2)		-
<3 times/day	5 (2.5)	1 (0.6)	4 (14.2)	0.001	28.3
Q9: Hiccups during or after feedings	18 (9)	6 (3.5)	12 (42.8)	<0.0001	20.6
≥6 times/day	1 (0.5)	0	1 (3.6)		-
3-5 times/day	5 (2.5)	0	5 (17.8)		-
<3 times/day	12 (6)	6 (3.5)	6 (21.4)	0.002	7.5
Q10: Cough during or after feeding	11 (5.5)	2 (1.1)	9 (32.1)	<0.0001	40
≥6 times/day	3 (1.5)	0	3 (10.7)		-
3-5 times/day	2 (1)	0	2 (7.2)		-
<3 times/day	6 (3)	2 (1.1)	4 (14.2)	0.003	14.8
Q11: Frequency of URTI within the 6 months					
1-3 times	175 (87.9)	153 (89.5)	22 (78.5)	0.11	0.4
4-6 times	21 (10.5)	17 (9.9)	4 (14.2)	0.50	1.5
>6 times	3 (1.5)	1 (0.6)	2 (7.2)	0.05	13
Q12: Growling outside the common-cold or flu-like symptoms	16 (8)	8 (4.6)	8 (28.5)	0.0003	8.5
1-3 times	11 (5.5)	5 (2.9)	6 (21.4)	0.0001	9.5
4-6 times	3 (1.5)	3 (1.7)	0		-
≥6 times	2 (1)	0	2 (7.2)		-

Table II. Reflux symptoms in infants in Menderes district

Q13: Hoarseness outside URTI within the 6 months?	4 (2)	2 (1.1)	2 (7.2)	0.037	6.5
1-3 times	4 (2)	2 (1.1)	2 (7.2)	0.07	6.5
4-6 times	0	0	0		-
≥6 times	0	0	0		-
Q14: Having lower respiratory tract problems within the 6 months	37 (18.5)	32 (18.7)	5 (17.8)	0.914	0.9
1-3 times	37 (18.5)	32 (18.7)	5 (17.8)	0.914	0.9
4-6 times	0	0	0		-
≥6 times	0	0	0		-
Q15: Wetting the pillow during sleeping	30 (15)	22 (12.8)	8 (28.4)	0.04	2.7
Everyday	24 (12)	20 (11.7)	4 (14.2)	0.75	1.2
3-6 days/week	1 (0.5)	0	1 (3.5)		-
<3 days/week	5 (2.5)	2 (1.1)	3 (10.7)	0.02	10.1
Q16: Problem in weight gain within the 6 months?	47 (23.6)	38 (22.2)	9 (32.1)	0.252	1.6

increased upper respiratory infection rate within 6 months (>6 times) were more common in infants with GERD.

As in Salvatore's study; reflux score according to our questionnaire had week correlation with acid exposure measured by 24-hour pH study (8). It is possible to diagnose an infant with GERD using questionnaires, but, the main problem both with our questionnaires and previous ones was the lack of a patient control group. There must be a patient control group including infants who had vomiting due to other causes such as urinary tract infection, gastroenteritis, sinusitis or otitis.

For this reason, cut-off values for the diagnosis of GERD should be increased and then a strong correlation may be found with acid exposure. Further studies with "patient control group" and gold standard diagnostic techniques such as "multi-channel intra-luminal impedance" analyses are needed for the development of the ideal questionnaire form for the infants. But, the use of multi-channel intra-luminal impedance to diagnose GERD in all infants is unnecessary too expensive for our country.

The prevalence of GERD in infants in our study based on the reflux disease questionnaire was found to be 14% (n=28/199). It was more common in younger infants, and a longer period of breastfeeding had a protective effect. Environmental factors such as number of siblings and passive smoking did not have any impact on the presence of GERD. It is difficult to compare our results with previous reports due to different diagnostic methods. In general population, the prevalence of GERD symptoms in infants is in the range of 1-10% (17). It was found to be 8%, as documented by pH monitoring in a population of unselected infants (18). In some reports; it was estimated to be approximately 18% in infants, which shows an increase in diagnosis (19).

Yalcin SS et al. similarly mentioned the protective effect of breastfeeding on the infant's crying, regurgitation and short sleeping periods in a recent report (20). The main mechanism for the protective effect of breastfeeding is not exactly known. It was shown that breastfed and formula-fed infants had similar frequency of physiological GER although the duration of reflux episodes measured by pH probe might be shorter in breastfed infants. It is a well known fact that the standard commercial formula fortified with iron has a different fat and protein content and 46% higher osmolality than human milk. This may cause both delayed gastric emptying and prolonged gastric distention and may predispose to GER in infants (1). Although we could not find any significant difference in the frequency of passive smoking in infants with or without GERD, it was seen that passive tobacco exposure contributes to the development of GER in infants particularly with apparent life-threatening effects (21). The esophageal pH parameters were found to be markedly elevated in the passive smoking exposure group compared to non-exposed infants. In addition, a linear relationship was found between the number of cigarettes smoked per day by the mother and the incidence of gastroesophageal reflux >5 minutes/hour in a 24-hour recording. Passive smoking also increases the persistence of reflux symptoms from infancy to 9 years of age (22).

In conclusion, we developed and validated a novel GERD questionnaire form to use in infants (<24 months of age), and we found that the prevalence of GERD was 14%. This form may be used in pediatric and pediatric gastroenterology outpatient clinics for the assessment of GERD in infants.

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Appendix 1. Gastroesophageal reflux questionnaire for Turkish infants (Sm reflux questionnaire)

Question	Points	
1. Does your baby vomit?	No ---------->	3rd question
	Yes	
	1-2 times/day	1
	3-5 times/day	2
	> 5 times/day	3
2. How is your baby vomiting?	Regurgitating	1
	Belching	1
	Gagging	2
3. Does the baby cry during or after feeding?	No	0
	Yes	
	≥ 6 times/day	3
	3-5 times/day	2
	< 3 times/day	1

Appendix 1. Gastroesophageal reflux questionnaire for Turkish infants (Sm reflux questionnaire)

Question	Points	
4. Does the baby refuse feedings even hungry?	No	0
	Yes	
	≥ 6 times/day	3
	3-5 times/day	2
	< 3 times/day	1
5. Does your baby have cyanosis (turned purple or blue) during or after feeding?	Yes	1
	No	0
6. Does your baby arching back during or after feeding?	Yes	1
	No	0
7. Does your baby have irritability or fussiness such as crying and grimacing outside the feeding?	No	0
	Yes	
	≥ 6 times/day	3
	3-5 times/day	2
	< 3 times/day	1
8. Does your baby have the behavior of chewing or swallowing outside the feeding?	No	0
	Yes	
	≥ 6 times/day	3
	3-5 times/day	2
	< 3 times/day	1
9. Does your baby have episodes of hiccups during or after feedings?	No	0
	Yes	
	≥ 6 times/day	3
	3-5 times/day	2
	< 3 times/day	1
10. Does your baby cough during or after feeding?	No	0
	Yes	
	≥ 6 times/day	3
	3-5 times/day	2
	< 3 times/day	1
11. How often does your baby have upper respiratory system infections (common-cold, flu-like symptoms) within the 6 months?	1-3 times	0
	4-6 times	1
	> 6 times	2
12. Does your baby have growling (wheezing) outside the common-cold or flu-like symptoms?	No	0
	Yes	
	1-3 times	1
	4-6 times	2
	≥ 6 times	3
13. Does your baby have hoarseness without having common-cold or flu-like symtoms within the 6 months?	No	0
	Yes	
	1-3 times	1
	4-6 times	2
	≥ 6 times	3

Appendix 1. Gastroesophageal reflux questionnaire for Turkish infants (Sm reflux questionnaire)		
Question	**Points**	
14. Does your baby have lower respiratory tract problems such as bronchitis or pneumonia within the 6 months?	No	0
	Yes	
	1-3 times	1
	4-6 times	2
	≥ 6 times	3
15. Does your baby wetting the pillow during sleeping?	No	0
	Yes	
	Everyday	3
	3-6 days/week	2
	< 3 days/week	1
16. Does your baby have trouble gaining enough weight within the 6 months?	Yes	1
	No	0