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Diagnostic Efficacy of Distal Esophagus Ultrasonography in Diagnosis of Gastroesophageal Reflux Disease in Children

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Abstract: To evaluate the diagnostic efficacy anatomical measurements of distal esophagus by ultrasonography in diagnosis of gastroesophageal reflux in children. All children suspicious to Gastroesophageal Reflux Disease (GERD) according to clinical history and physical examination who were indicated for further studiy with endoscopy and esophageal biopsy (as the gold standard) and without known history or current ulcer were considered to enter the study. An ultrasonographic study (3.5 MHz probe (Aloka1700, Japan)) did for all patients and 6 anatomical parameters (including the esophageal diameter, esophageal wall thickness, esophageal mucosal thickness, hiatal diameter, subdiaphragmatic esophageal length and gastric wall thickness) were measured in the ultrasound. Then the patients underwent an upper gastrointestinal endoscopy and esophageal biopsies were taken. The histopathologic criteria for GERD were erythema, ulcer, barret esophagus and leukocyte infiltration. According to the sonographic and histopathologic results, for all measurements, we plotted the receiving operative characteristics (ROC) curve to assess the area under the curve (AUC) as an indicator for diagnostic efficacy. For the best variables, we selected cut off points and then calculated the diagnostic indices (including sensitivity, specificity, positive and negative redictive values). Totally 103 (57 patients (mean age of 4.7±3.5 years) and 46 controls (mean age of 5.2±3.9 years)) entered the study. The mean esophageal diameter was 12±2.7 mm (6-17) in patients and 10.1±2.4 in controls; the mean sub diaphragmatic esophageal length was 15.9±6.3 mm in patients and 22.2±9.9 in controls (both $p<0.0001$). Except for Gastric wall thickness, other sonographic measures were statistically greater in patients (all Ps = 0.016) Computing AUC of 6 variables revealed all of them are equal or >0.63 (all $p<0.025$) and the highest value was for esophageal diameter and subdiaphragmatic esophageal length (both 0.71). Dividing esophageal diameter by subdiaphragmatic esophageal length yielded a new variable that its AUC was 0.76. Considering a cut-off point equal to 7 mm for esophageal diameter yielded a sensitivity of 0.96 while for cut-off point of 14.5 yielded a specificity of one. Considering a cut-off point equal to 10 mm for subdiaphragmatic esophageal length yielded a specificity of 0.93 while for cut-off point of 0.3 yielded a sensitivity of 0.98. Considering a cut-off point equal to 7 mm for esophageal diameter divided by subdiaphragmatic esophageal length yielded a sensitivity of 1, while for cut-off point of 1.5 yielded a specificity of 0.96.

Key words: Gastroesophageal reflux, children, ultrasonography

INTRODUCTION

Nearly all healthy individuals experience Gastroesophageal Reflux (GER) in their life (Jang *et al*., 2001) and the most common cause of intermittent regurgitation or vomiting occurring since birth is GER (Blumer *et al*., 2004). When the episodes of GER are frequent and severe, this pathologic process is called Gastroesophageal Reflux Disease (GERD) (El Mouzan *et al*., 2001). GERD is common among children specially infants (Ashorn *et al*., 2002) and causes irritability, frequent vomiting, apnea, failure to thrive, esophagitis, asthma and reactive airway, chronic cough, recurrent and aspiration pneumonia, reduced pulmonary function and sudden infant death syndrome (Jang *et al*., 2001; Omari *et al*., 2002; Koumanidou *et al*., 2004).

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Thus, there is an increasing need for a screening and diagnostic method, especially in infancy (Koumanidou *et al*., 2004).

Some diagnostic methods have been used for GERD diagnosis such as pH monitoring, barium meal, manometry, sonography, radionuclide scanning of the upper gastrointestinal tract and endoscopic biopsy (Koumanidou *et al*., 2004; Ashorn *et al*., 2002). Many authors believe the pH monitoring as the preferred gold standard of the diagnosis and quantification of acid reflux (Jang *et al*., 2001; Blumer *et al*., 2004; Koumanidou *et al*., 2004) meanwhile, some others discuss against the role of pH monitoring in determining of GERD severity (Ashorn *et al*., 2002).

Although, the pH monitoring, manometry and gastroesophageal junction scintigraphy are more sensitive than sonography but could not provide morphologic data of the lower esophageal sphincter and esophagous (Koumanidou *et al*., 2004). Sonography as a non-invasive, cheap and readily available method could be described informative, accurate and sensitive technique in the diagnosis of GER in infants and children (Koumanidou *et al*., 2004; Blumer *et al*., 2004; Kacar *et al*., 2007) that provides morphologic and functional information (Koumanidou *et al*., 2004; Blumer *et al*., 2004).

However, some limitations remain, for example poor depiction of the intrathoracic esophagus and the esophageal defense mechanisms. Sonographic diagnosis of GERD is mainly based on the visualization of the gastric fluid passage into the abdominal esophagus and the clearance of refluxed material by esophageal peristalsis (Koumanidou *et al*., 2004; Blumer *et al*., 2004). In this relation, color Doppler sonography is also used (Blumer *et al*., 2004; Jang *et al*., 2001) that has increased the diagnostic sensitivity of the method from 94.4-95.5%. These two methods have shown a good correlation with pH monitoring (Jang *et al*., 2001; Koumanidou *et al*., 2004).

Other sonographic findings have been proposed for GERD diagnosis that includes measurement of abdominal esophagus length and assessment of GE junction (Koumanidou *et al*., 2004; Kacar *et al*., 2007). As abdominal esophagus length is related to GERD, its accurate assessment could be useful in GERD diagnosis. It has been postulated that abdominal esophagus length is directly associated with the capacity for reflux prevention (Koumanidou *et al*., 2004). Regarding pathophysiologic process and mechanism of GERD, some other anatomical assessments such as esophageal mucosal diameter could be important in the diagnosis of the disease too. Considering these facts, in the current study, we have assessed the diagnostic accuracy of some sonographic anatomical measurements of the esophagous for diagnosis of the GERD.

PATIENTS AND METHODS

Patients' selection: All children suspicious to gastroesophagial reflux disease (GERD) according to clinical history and physical examination referred to the gastrointestinal clinic of the children's medical center hospital (Tehran University of Medical Sciences) were initially considered. All patients were <14 years old. Among these patients, all cases that were indicated for further study with endoscopy and esophageal biopsy (as the gold standard) (with or without pH monitoring) were considered to enter the study.

Patients with known history of gastric or duodenal ulcer or with proved ulcer in endoscopy were excluded from the study. Also all patients that used prokinetic and anti acid drugs 24 h prior to sonography were excluded from the study. Other exclusion criteria were as follow:

- Presence of any systemic or metabolic disease.
- History of any obstructive gastrointestinal disorder.
- Use of any drugs 24 h before endoscopy.

All patients signed a written informed consent and the study was approved by ethics committee of the university.

An ultrasonographic study did for all patients who were selected according to the above mentioned inclusion and exclusion criteria. Then the patients underwent an upper gastrointestinal endoscopic study up to 24 h after ultrasound and esophageal biopsies were taken. According to the endoscopy and histopathologic results, the patients were categorized in two groups of disease positive or patients and disease negative or controls.

Ultrasonography: All patients underwent an ultrasonographic study of the gastroesophageal junction and distal esophagus one day before to endoscopy.

During ultrasonography, the patients were awake while they were relaxed in rest position. After using sufficient fluid according to patient's age, such as milk or water, patients were studied in supine position with 3.5 MHz probe (Aloka1700, Japan). The stomach and lower segment of esophagus were studied. Also, the esophageal diameter, esophageal wall thickness, esophageal mucosal thickness, hiatal diameter, subdiaphragmatic esophageal length and gastric wall thickness were measured for all cases.

Endoscopy: The endoscopy device was Pentax EPM 3300 EG 2731, Japan. The endoscopy diameter was 6.8mm or 7.6mm that was adjusted according to patient's age. For sedation, we used intravenous (0.1 mg kg^{-1} stat) or oral (0.2-0.3 mg kg^{-1}) Midazolam. For histopathologic evaluation, we took at least three samples from the lower third of esophageal mucosa. The criteria for disease positive group or patients were histopathologic findings confirming the GERD including erythema, ulcer, barret esophagus and leukocyte infiltration in different layers of the esophagus and disease negative or controls were considered when above mentioned histopathologic findings confirming the inflammatory responses of the GERD in esophagus were absent.

Statistical analysis: Statistical analysis was done by SPSS ver.11.5 (Chicago, IL, USA).

We used the t-test for comparing means between two groups. Also we used chi-square (χ^2) for comparing nominal variables.

According to the sonographic and histopathologic results, for all 6 previously mentioned variables, we plotted the Receiving Operative Characteristics (ROC) curve to assess the area under the curve as an indicator for diagnostic efficacy of that variable for differentiation of the GERD form non GERD patients. For the variables which had the highest area under the curve, we selected different cut off points and then calculated the diagnostic indices (including Sensitivity (Se), Specificity (Sp), Positive Predictive Value (PPV), Negative Predictive Value (NPV), Positive Likelihood Ratio (PLR) and Negative Likelihood Ratio (NLR)) for each cut off point. All $p<0.05$ were considered as statistically significant.

RESULTS

Totally 103 children were entered in the study; 57 of them were patients (55.3%) and 46 were controls (44.7%). Mean age of patients was 4.7±3.5 years (4.5 month-13 years) and the mean age of controls was 5.2±3.9 years (2 months-13.5 years) ($p = 0.46$). Among patients, totally 37 were male (64.9%), while among controls, totally 21 were male (45.7%) ($p = 0.051$). The most common symptom in patients was vomiting seen in 39 patients (68.4%). Other symptoms, signs and important laboratory findings are mentioned in Table 1.

The mean age at symptoms onset was 1.5±1.7 months (2 weeks to 5 months) among patients. The mean birth weight was 3.2±0.5 kg (1.7-4.1 kg) and the mean current weight was 16.4±9 kg (4.5-45 kg) among patients. The mean symptoms duration was 1.8±2.5 months (1 week-8 months).

Table 1: Symptoms and signs in patients

Anorexia	37(64.9%)
Vomiting	39(68.4%)
GI bleeding	4(7%)
Esophageal stenosis	4(7%)
Weight loss	30(52.6%)
Chronic cough	29(50.9%)
Wheezing	27(47.4%)
History of aspiration pneumonia	16(28.1%)
Apnea	1(1.8%)
Iron deficiency anemia	35(61.4%)
Sandifer syndrome	6(10.5%)

Table 2: Comparison of the anatomical measurements between patients and controls

Sonographic measurement	Group	Mean±S.D.	p-value
Esophageal diameter	Case	12.0±2.7	<0.0001
	Control	10.1±2.4	
Esophageal wall thickness	Case	4.9±1.8	0.003
	Control	4.0±1.3	
Esophageal mucosal thickness	Case	2.8±1.2	0.016
	Control	2.2±1.5	
Hiatal diameter	Case	14.0±3.8	0.01
	Control	12.0±3.5	
Subdiaphragmatic esophageal length	Case	16.0±6.3	<0.0001
	Control	22.2±10.0	
Gastric wall thickness	Case	3.0±4.0	0.87
	Control	2.9±4.6	

The severity of disease according to clinical findings was mild in 15 patients (26.4%), moderate in 30 patients (52.6%) and severe in 12 patients (21%).

In the gross endoscopy evaluation, the severity of the disease was mild in 11 patients (19.3%), moderate in 36 patients (63.2%) and severe in 10 patients (17.6%).

In the sonographic evaluation, the mean esophageal diameter was 12±2.7 mm (6-17) in patients and 10.1±2.4 in controls ($p<0.0001$). The mean sub diaphragmatic esophageal length was 15.9±6.3 mm in patients and 22.2±9.9 in controls ($p<0.0001$). Other sonographic measurements of patients were statistically greater than controls other than gastric wall thickness that was statistically equal in two groups (Table 2).

The sonographic reflux was seen in 43 patients (75.4%) and in one control (2.2%) ($p<0.0001$).

For differentiation of patients from controls according to sonographic measurements (6 mentioned variables), we plotted the receiver operating characteristics (ROC) curve for each variables. The area under the curve was considered for all 6 variables as an index of test efficacy. For esophageal diameter, the AUC was 0.71 (95% confidence interval (CI) = 0.61-0.81) ($p<0.0001$) and for sub diaphragmatic esophageal length, the AUC was 0.71 (95% CI = 0.61-0.82) ($p<0.0001$). For all other variables, the area under the curve was statistically significant (Table 3).

Statistical analysis showed no difference for all pair wise comparisons of these variables for differentiation of the reflux patients ($p>0.05$).

Table 3: Roc curve analysis results for anatomical measurements in differentiating patients

Variable	Area under the curve	p-value	95% confidence interval
Esophageal diameter	0.71	<0.0001	0.61-0.81
Esophageal wall thickness	0.68	0.002	0.57-0.78
Esophageal mucosal thickness	0.68	0.002	0.57-0.78
Hiatal diameter	0.64	0.015	0.53-0.75
Sub diaphragmatic esophageal length	0.71	<0.0001	0.62-0.82
Gastric wall thickness	0.63	0.025	0.52-0.74
Esophageal diameter by sub diaphragmatic esophageal length	0.76	<0.0001	0.67-0.84

Table 4: Diagnostic indices of the selected cut-off points for three anatomical measurements of

	TP	FN	TN	FP	Se. (95% CI)	Spe. (95% CI)	PPV (95% CI)	NPV (95% CI)	PLR (95% CI)	NLR (95% CI)
A* >=7	55	2	6	40	0.96 (0.88-0.99)	0.13 (0.05-0.26)	0.58 (0.47-0.68)	0.75 (0.35-0.97)	1.1 (0.98-1.3)	3.7 (0.79-17.6)
A >=9	50	7	14	32	0.88 (0.76-0.95)	0.30 (0.18-0.46)	0.61 (0.50-0.72)	0.67 (0.43-0.85)	1.3(1.0-1.6)	2.5 (1.1-5.6)
A >=11	38	19	32	14	0.67 (0.53-0.79)	0.70 (0.54-0.82)	0.73 (0.59-0.84)	0.63 (0.48-0.76)	2.2 (1.4-3.5)	2.1 (1.4-3.2)
A >=13	17	40	41	5	0.30 (0.18-0.43)	0.89 (0.76-0.96)	0.77 (0.55-0.92)	0.51 (0.39-0.62)	6.5 (2.8-15)	3 (2-4.5)
A >=14.5	10	47	46	0	0.18 (0.09-0.30)	1 (0.92-1)	1 (0.69-1)	0.49 (0.39-0.60)	--	1.2 (1.1-1.4)
B** <=10	7	50	43	3	0.12 (0.05-0.24)	0.93 (0.82-0.99)	0.70 (0.35-0.93)	0.46 (0.36-0.57)	1.9 (0.51- 6.9)	1.1 (0.9-1.2)
B <=13	24	33	35	11	0.42 (0.29-0.56)	0.76 (0.61-0.87)	0.69 (0.51-0.83)	0.51 (0.39-0.64)	1.8 (1-3.2)	1.3 (1-1.7)
B <=18	43	14	29	17	0.75 (0.62-0.86)	0.63 (0.48-0.77)	0.72 (0.59-0.83)	0.67 (0.51-0.81)	2 (1.4-3.1)	2.6 (1.5-4.3)
B <=25	53	4	16	30	0.93 (0.83-0.98)	0.35 (0.21-0.5)	0.64(0.53-0.74)	80 (0.56-0.94)	1.4 (1.1-1.8)	5 (1.8-13.8)
B <=30	56	1	8	38	0.98 (0.91-0.99)	0.17 (0.08-0.31)	0.60 (0.49-0.70)	0.89 (0.52-0.99)	1.2 (1-1.4)	9.9 (1.3-76.4)
C*** >=0.3	57	0	8	38	1 (0.93-1)	0.17 (0.08-0.31)	0.60 (0.49-0.70)	1 (0.63-1)	1.2 (1.1-1.4)	-
C >=0.5	50	7	25	21	0.88 (0.76-0.95)	0.54 (0.39-0.69)	0.70 (0.58-0.81)	0.78 (0.60-0.91)	1.9 (1.4-2.7)	4.4 (2.1-9.3)
C >=0.65	39	18	34	12	0.68 (0.55-0.80)	0.74 (0.59-0.86)	0.76 (0.63-0.87)	0.65 (0.51-0.78)	2.6 (1.6-4.6)	2.3 (1.5-3.6)
C >=0.8	28	29	39	7	0.49 (0.36-0.63)	0.85 (0.71-0.94)	0.80 (0.63-0.92)	0.57 (0.45-0.69)	3.2 (1.6-6.7)	1.7 (1.3-2.2)
C >=1.5	5	52	44	2	0.08 (0.03-0.19)	0.96 (0.85-0.99)	0.71 (0.29-0.96)	0.46 (0.36-0.56)	2 (0.4-9.9)	1 (0.95-1.2)

*(A) esophageal diameter, **(B) sub diaphragmatic esophageal length and ***(C) esophageal diameter by sub diaphragmatic esophageal length

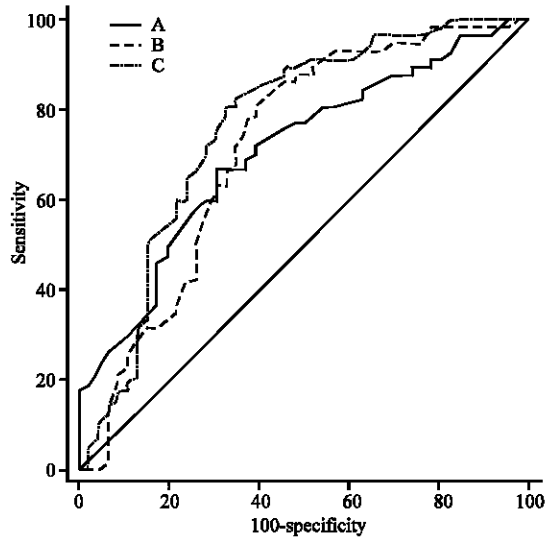

Fig. 1: ROC curves of best three anatomical measurements

For sub diaphragmatic esophageal length, the relation between presence of the disease and the length was reverse; as the length decreased, the probability of the disease increased.

As the highest AUC's were for the esophageal diameter and sub diaphragmatic esophageal length, we calculated a new variable with esophageal diameter divided by subdiaphragmatic esophageal length and then calculated the AUC for this new variable that was 0.76 (95% CI = 0.66-0.86) (p<0.0001). This value was higher than all AUC's but the difference was not statistically significant with esophageal diameter and sub diaphragmatic esophageal length (p = 0.25 and p = 0.092, respectively). We considered these 3 highest AUC variables for the subsequent analysis; i.e., esophageal diameter, sub diaphragmatic esophageal length and mentioned new variable calculated via esophageal diameter by sub diaphragmatic esophageal length (Fig. 1).

In the Table 4, the diagnostic indices of selected cut off points of esophageal diameter, sub diaphragmatic esophageal length and esophageal diameter divided by sub diaphragmatic esophageal length for diagnosis of reflux are mentioned.

DISCUSSION

Gasteroesophageal reflux (GER) occurs during the life of most peoples especially in the childhood and newborn period; when it occurs frequently and make pathologic symptoms and signs, it refers to Gastroesophageal Reflux Disease (GERD). Different methods are introduced for diagnosis of the disease during childhood including barium meal, PH monitoring, manometry, radionucleide scan, endoscopic biopsy and sonography (Ashorn *et al*., 2002; Koumanidou *et al*., 2004). Sonography is the least invasive and the most feasible method among these tools. It has been shown that the sensitivity of PH monitoring, manometry and radionucleide scan is higher than sonography, instead, these methods unlike to the sonography, could not yield any information about the anatomical characteristics of the distal and intraabdominal

part of esophagus (Koumanidou *et al*., 2004). Sonographic diagnosis of GERD has mainly based on detection of the returning gastric fluid to esophagus (2); in this relation, the Doppler study has increased the sensitivity of the method (Koumanidou *et al*., 2004).

It has been well known in adult patients that the anatomical situation of the distal and intraabdominal part of the esophagus is very important in the pathophysiology of the GERD; accordingly, the subdiaphragmatic portions that are <2 cm have been highly associated with the GERD (De Meester *et al*., 1979).

Thus, evaluation of this part could be of value in detection of the GERD in children. In the other hand, persistent irritation of the distal esophagus with the regurgitant fluid of the stomach could make inflammation in this area resulting the thickened esophageal wall and mucosa. Regarding these points, anatomical assessment of the related indices of the distal esophagus, could help us in diagnosis of the GERD. This was the basis of current study to evaluate the diagnostic efficacy of these anatomical measurements. Some of these measurements have net been noticed today, the others have been noticed only in limited studies (Koumanidou *et al*., 2004; Esposito *et al*., 2001). The most evaluated index is the subdiaphragmatic esophageal length (Koumanidou *et al*., 2004; Gomes *et al*., 1993).

Koumanidou *et al*. (2004) compared abdominal esophagus length between 150 healthy with 108 GERD neonates or infants. All GERD patients had a history of regurgitation or intermittent vomiting associated in most patients with asthma, chronic cough, failure to thrive or recurrent pneumonia. While, the presence of GERD had been shown sonographically, all of them were confirmed by barium meal or PH monitoring. They found the abdominal esophagus length is lower in neonates and infants with GERD in comparison to healthy neonates and infants (Koumanidou *et al*., 2004). Furthermore, considering the fifth percentile point of children without reflux as cut off point, they found the sensitivity and specificity of abdominal esophagus length measurement for diagnosis of GERD is equal to 94%. They didn't use the ROC curve analysis to calculate the diagnostic indices of the measurement for different cut off points but considering their sensitivity and specificity in the certain selected cut off point, it seems that their diagnostic efficacy is higher than current study. One important point in this study is the study design. As they selected the patients in a case-control design, this could be the reason of this difference. Generally, when in an evaluation of test study, the patients are being selected based on presence of the disease that has been confirmed by gold standard and controls are being selected among the healthy persons (this design is named case-control design for such studies), this could be increase the efficacy indices of the test (i.e., sensitivity, specificity and other indices) for diagnosing disease. The reason originates from this fact that in such designs, the negative disease group (controls) is selected from healthy peoples that don't have the disease and thus, their test results show a significant difference with disease positive group (cases). It is obvious in such conditions, selecting the extreme cases from the disease negative group and thus greater differences between 2 group could increase the diagnostic indices of the test in comparison to the conditions that the disease positive and disease negative groups are selected based on the presence of certain symptoms and signs in a real clinical setting.

As it mentioned, we couldn't find any study similar to current study to assess the ROC curve analysis for diagnostic efficacy of sonographic anatomical measurements of distal esophagus for diagnosis of GERD. As we could see, the diagnostic efficacy of the ultrasound for this purpose is acceptable; for esophageal diameter, the cut off point of 11 mm shows a Se. of 0.67 and Spe. of 0.70, the cut off point of 18 for subdiaphragmatic esophageal length (measures <18 mm), the Se. is 0.75 and Spe. is 0.63 and for esophageal diameter by sub diaphragmatic esophageal length, the cut off point of 0.65 shows the Se. of 0.68 and Spe. of 0.74; for latter variable, the cut off point of 0.3 shows a Se. and NPV equal to 1 means all of the patients with GERD have a variable >0.3 or if the patient have a result <0.3, he/she would not have GERD. Another point of the table is the cut off point of 14.5 for esophageal diameter; if the patient has a measurement greater than this value, he/she would have GERD (Spe. and PPV of 1 in this value). These figures could help the clinician in diagnosis of the GERD in patients.

CONCLUSION

It seems that gray scale ultrasonographic anatomical measurements of distal esophagus (especially esophageal diameter and sub diaphragmatic esophageal length) could be of value in diagnosis of GERD in children.

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