ORIGINAL ARTICLE

Prevalence, Clinical Predictors and Diagnosis of Gastro-oesophageal Reflux in Children with Persistent Respiratory Symptoms

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Summary

Objectives: This was a cross sectional study conducted in the Paediatric Institute among infants and children with chronic respiratory symptoms with the following objectives:

i) to determine the prevalence of gastro-oesophageal reflux in children with persistent respiratory symptoms
ii) to identify the clinical predictors of GOR (Gastro-oesophageal reflux) in children with persistent respiratory symptoms and
iii) to assess the validity of abdominal ultrasound, barium oesophagogram and chest radiograph in diagnosing GOR in these patients.

Materials and Methods: Forty-four patients were recruited over a period of six months. All the presenting symptoms were identified. The patients were subjected to chest radiograph, abdominal ultrasound, barium oesophagogram and 24-hour pH oesophageal monitoring.

The predictive validity of clinical symptoms, chest radiograph, abdominal ultrasound and barium oesophagogram were assessed. Twenty-four hours oesophageal pH was the gold standard to diagnose GOR.

Results: The mean age of patients was 9.1 months (1 - 58 months). Thirty-one patients (70.5%) were confirmed to have GOR by pH study. Respiratory symptoms alone were not useful to predict GOR. Cough had the highest sensitivity of 51.6%. Stridor, wheeze and choking each had a specificity of 76%. Wheeze, vomiting, choking and stridor were identified to have high specificity (90 - 100%) in diagnosing GOR when any two symptoms were taken in combination.

Collapse/consolidation was the commonest radiological abnormality but had low sensitivity (35.5%) and specificity (53.8%). However hyperinflation on chest radiograph had a specificity of 92.3% with positive predictive value of 80% in diagnosing GOR. Barium oesophagogram has low sensitivity (37.9%) and moderate specificity (75%) in diagnosing GOR in children with respiratory symptoms.

Abdominal ultrasound was a valid mode of diagnosing GOR when there were three or more reflux episodes demonstrated during the screening period with a specificity of 90.9%. However the sensitivity was low i.e. 20 - 25%. The specificity increased to 90 - 100% when two positive tests were taken in combination (abdominal ultrasound

and barium oesophagogram). However the sensitivity remained low (10 - 20%). Chest radiograph did not improve the predictive value when considered with the above tests. Combination of clinical symptoms were useful as clinical predictors of GOR. In the absence of a pH oesophageal monitoring, a combination of barium oesophagogram and ultrasound may be helpful in diagnosing GOR.

Key Words: Gastro-oesophageal reflux, Clinical Predictors, Validity, pH oesophageal monitoring, Ultrasound, Barium oesophagogram

Introduction

The relationship between GOR (Gastro-oesophageal reflux) and respiratory disease was first recognised in the late 19th Century[1]. Previous studies have shown that the prevalence of GOR in patients with chronic respiratory disorder is between 47 - 63%[2]. GOR may cause a variety of respiratory symptoms. Chronic aspiration is believed to be the most likely cause of respiratory symptoms. Aspiration of tracheobronchial secretions of liquid gastric contents may trigger cough, wheeze and recurrent pulmonary diseases such as pneumonia, lung abscess and so called near missed SIDS[1]. There are other various mechanisms that may result in respiratory symptoms such as reflex bronchospasm, reflex central apnoea and reflex bradycardia[3,4].

Likewise, respiratory disorders such as chronic cough or an asthmatic attack may induced reflux resulting in a vicious cycle. Respiratory function that increases abdominal pressure and negative intrathoracic pressure, reduction in the lower oesophageal sphincter pressure or increase gastric production may potentiate GOR. This may be worsened by bronchodilators such as theophylline and beta sympatomimetics. There must be a high index of suspicion to diagnose GOR. In many children with classical symptoms, history is helpful. In the absence of symptoms, GOR needs to be ruled out by further studies.

The evaluation of GOR ideally should demonstrate the presence or absence of reflux and the association of reflux as a cause of the child's symptoms[3]. Twenty-four hours pH oesophageal monitoring is considered to be the most reliable method for diagnosing reflux[5,6,7]. Other diagnostic examinations are upper gastrointestinal studies, abdominal ultrasound, endoscopy and oesophageal biopsy, bronchoscopy to detect lipid laden macrophages (LLMS) in the bronchial aspirate, scintigraphic study and oesophageal manometery. The sensitivity and specificity of these tests are low and does not correlates with patient's symptoms[1].

Barium oesophagogram is the oldest and most available clinical tests of oesophageal function[8]. However the incidence of false positives and negative results are high making it less valuable to diagnose GOR[9,10] which may be missed in 40% of patients.

Ultrasound is a non invasive method of detecting GOR. Riccabona *et al*[6] compared ultrasound to pH metry in evaluating the accuracy of sonography in the early diagnosis of GOR in 30 children and the results showed that the specificity was 87.5% and the sensitivity was 100%. However this test is operator dependent.

Endoscopy with oesophageal biopsy is not routinely done. It does not diagnose GOR but allows direct visualisation of oesophageal mucosa and biopsy to detect the severity of reflux oesophagitis[9,11]. Twenty-four hour pH oesophageal monitoring is widely accepted to detect the presence of GOR with a reported sensitivity of 87% and specificity of 93%[5,8]. It allows prolonged periods of observations under near normal conditions. The prolonged nature of the study allows for accurate diagnosis to be made. In addition to aiding the diagnosis, it has a predictive value in identifying patients that are unlikely to respond to medical treatment. Although pH oesophageal monitor is the gold standard in diagnosing GOR, the test is expensive and not readily available locally. No studies have been performed to assess the validity of barium and ultrasound in diagnosing GOR.

Therefore this study was undertaken to determine the prevalence of GOR in children with persistent respiratory symptoms ii) to identify the clinical predictors of GOR in children with persistent respiratory symptoms and to iii) assess the validity of ultrasound, barium oesophagogram and chest radiograph in diagnosing GOR.

Materials and Methods

This was a cross-sectional study conducted for a period of six months at Paediatric Institute, Kuala Lumpur. The study populations consisted of infants and children aged one to 58 months (mean 9.1 months) with chronic respiratory symptoms such as wheeze, recurrent aspiration, recurrent chest infection and stridor. These patients were referred to UKM Respiratory Unit for further investigative procedures when their respiratory symptoms had not responded to therapeutic measures undertaken by the Paediatrician in charge.

Relevant birth, neonatal and family history, presenting symptoms particularly related to GOR were recorded in the study protocol. Symptoms recorded were persistent cough, wheeze, stridor, apnoea and other feeding related symptoms such as vomiting, regurgitation and choking. When appropriate, investigations to exclude other diagnoses such as skin allergy tests in patients with recurrent wheeze, Mantoux test and tuberculous culture in patients with chronic cough. In patients with recurrent pneumonia, diagnosis of cystic fibrosis or immunodefeciency was excluded by normal sweat chloride tests and normal levels of immunoglobulins. Bronchoscopy and echocardiography were performed in patients with stridor to exclude abnormality of the airways or presence of anomalous vessels. Underlying cardiac lesions were identified for those with cardiac murmurs by echocardiogram. All chests radiographs were reviewed by a Paediatric Radiologist.

All patients were subjected to ultrasound, barium oesophagogram and pH oesophageal monitoring. Prior to the tests, the childrens' mothers/carers were instructed to discontinue prokinetic drugs for 48 hours. Ultrasound was performed by a Paediatric Radiologist. The patients were fasted three to four hours prior to the procedure. After evaluating the stomach and pyloric morphometry and function, the children were fed with physiological amounts of milk and scanning was performed during drinking and continued for at least five to 10 minutes. Positive reflux is defined as the presence of to and fro movement of fluid into the oesophagus. The numbers of reflux episodes were recorded based on the study by Gomes and Menanteau[12], comparing ultrasound in 350 symptomatic infants with 300 asymptomatic babies, they defined ultrasound findings over 10 minutes as: normal: 0 reflux, pathological reflux: 1 - 3 refluxes, mild dysfunction: 3 - 6 refluxes and severe dysfunction: more than 6 refluxes. For this study any reflux episode reported by the Radiologists during the scanning period is taken as significant.

For barium oesophagogram, the children were fasted three to four hours prior to the procedure. They were given 60 - 120mls of barium to drink in supine position. The flow of barium was observed under fluroscopy over five minutes. The number and extent of reflux episodes into the oesophagus were noted. If the patient refluxed twice during a brief fluroscopy, or refluxed once with clear delay in oesophageal clearance, GOR was considered. There were no radiological studies that relate the level of refluxed barium in the oesophagogram to the severity of the disease. In this study positive reflux was defined as i) the return of barium from stomach into the thorax to a height equal to one third of the length of oesophagus or[13] ii) number of reflux episodes in five minutes more than the acceptable number for the age (Cleveland)[14].

The children were admitted for the pH studies. The devices used for the study were the Synectics Digitrapper system (Sweden). It is portable and battery operated with internal antimony electrode and external AG/AgCl skin reference electrode.

Before used and in between studies, the probes were sterilised by immersion in glutaryldehyde for half an hour. Then the probes were calibrated in vitro using standard buffer solutions (pH 7.0 and pH 1).

The procedures were explained to the parents and carers. The duration of the pH recordings should at least be 18 hours. No premedication was required prior to the study.

Each child's height or length was measured and the distance from the tip of the nose to the lower oesophageal sphincter (LES) was calculated using the Stobels's formula[15] i.e. length from nares to LES (cm) =5 + 0.253 x height (cm). A distance equal to 87% of the total length was calculated and marked on the pH probe which was then passed transnasally to this mark. The proper position of the probe was further confirmed by fluroscopy where the tip should lie over the third vertebral body above the diaphragm throughout the respiratory cycle or by chest radiograph where the probe should be situated in the middle oesophagus. The reference electrode was then securely applied using the contact gel on the chest and together with the pH probe were connected to the recorder.

During the study the patients consumed normal diet and performed daily activities. The mother or carer was instructed to record time of events such as the beginning and end of feeds, changes in position (supine, prone, upright) and time when events such as crying, coughing or vomiting occurred. When the study was completed the data in the electronic recorder was down loaded to the computer for analysis and storage. The indices of GOR were automatically calculated by the computer software (Esophagogram 9, Gastrosoft Inc) and consisted of i) the number of reflux episodes, ii) the number of reflux episodes greater than five minutes, iii) the duration of the longest reflux episodes iv) percentage of the time when pH was less than 4 (reflux index). A De Meester score of more than 14.72 was used by the software to define significant reflux. The score was calculated from the data of patients less than a year old where the data was analysed under 'infancy mode'. Beyond this age the data was analysed under the 'paediatric mode' and no reflux score was calculated. It was based on the percentage of time when pH was less than 4 (reflux index) was more than 5%[16].

Statistical analysis

The data was summarised in database 4. The 24 hours pH oesophageal monitoring was taken as the gold standard for diagnosing GOR. The analysis involved calculations of sensitivity, specificity, positive predictive value and negative predictive value for each clinical predictor and investigative procedure (ultrasound, barium oesophagogram and chest radiograph).

Results

A total of 44 patients with persistent respiratory symptoms were evaluated for GOR. There were 19 males (43%) and 25 females (56.8%). The mean age was 9.1 months (range 1 - 58 months). Thirty-one patients (31/44) were confirmed to have GOR by 24 hour pH oesophageal monitoring, giving a total prevalence of 70.5%. The prevalence of GOR among neurologically impaired children was 20.4% (9/13). There were 14 (31.8%) ex-preterm babies of which nine babies had respiratory distress syndrome. Only one child had bronchopulmonary dysplasia. Table I shows the patient's characteristics, prevalences of GOR and associated disorders.

Clinical symptoms

Twenty-two patients presented with persistent cough (50%), 20 (45.4%) had vomiting and regurgitation followed by persistent wheeze in 16 (36.3%) of them. Choking, stridor and apnoea were present in 25%, 20.4% and 13.6% respectively. Based on individual symptoms for prediction of GOR, persistent cough had the highest sensitivity of 51.6% followed by vomiting with 48.3%. Their specificities were 53.8% and 61.5% respectively. Persistent wheeze, stridor, apnoea and choking had low sensitivities but higher specificities of more than 76%. Among all symptoms, wheeze had the highest positive predictive value of 81.2%.

When two symptoms were combined the specificity and positive predictive value increased but not the sensitivity. The presence of any of these two symptoms together i.e. wheeze and vomiting, choking and wheeze, choking and stridor increased the specificity to 92.3%. Vomiting and stridor in combination increased the specificity to 100%. Table II shows the predictive validity of respiratory symptoms evaluated for gastro-oesophageal reflux.

Chest radiograph

Thirty one (70.5%) of the 44 patients showed abnormal radiological findings. Table III showed the various radiological changes on the chest radiographs. In evaluating the radiological changes as predictors for GOR, collapse/consolidation showed a sensitivity of 35.5% and specificity of 53.8% with positive predictive value of 64.7%. Hyperinflation was the least sensitive (12.9%) but the most specific (92.3%).

Table I
The Characteristics of 44 Patients with Persistent Respiratory Symptoms Evaluated for GOR

	No (%)	No (%) with GOR by pH Study
Age (month) range- 1 - 58 months		
Mean: 9.1	19 (43.2)	17 (38.6)
Sex: Male	25	14 (31.8)
Race: Malay	24 (54.5)	18 (40.9)
Chinese	11 (25.0)	6 (13.6)
Indian	3 (6.8)	2 (4.5)
Others	6 (13.6)	5 (11.4)
Total	44	31 (70.5)
Associated Disorder		
1.CNS disease	13 (29.5)	9 (20.4)
Cerebral palsy	9	6 (13.6)
CNS abnormality	2	2 (4.5)
Dysmorphism with CNS Involvement	2	1 (2.3)
2.Recurrent/unresolved pneumonia	11 (29.5)	6 (13.6)
3.Chronic wheezer	4 (9.1)	4 (9.1)
4.Airway abnormality	4 (9.1)	2 (4.5)
Tracheobronchomalacia	1	1
Choanal atresia	1	0
Subglottic stenosis	2	1
5.Chronic lung disease	3 (6.8)	3 (6.8)
BPD	1	1 (2.3)
Interstitial pneumonia	1	1 (2.3)
Bronchiolitis obliterans	1	1 (2.3)
6.Feeding problem	3 (6.8)	2 (4.5)
7.Congenital heart disease	2 (4.5)	1 (2.3)
8.Recurrent apnoea	2 (4.5)	2 (4.5)
9.Multiple disorders	2 (4.5)	2 (4.5)
Total	44	31(70.5)

Barium oesophagogram

Forty one patients underwent barium oesophagogram of which 14 (34.1%) showed positive reflux. In predicting GOR, the sensitivity was 37.9%, specificity was 75% with a positive predictive value of 78.5%. Three patients did not turn up for the procedure.

Ultrasound

Forty-one patients were subjected to abdominal ultrasound. Three patients missed their appointment dates. Nineteen patients (46.3%) showed no reflux episodes during the screening period but 15 of them were confirmed to have significant reflux on pH study. Twenty-two (53.6%) patients had at least one documented reflux episode. This gave a sensitivity of 50%, a specificity of 36.3% and a positive predictive value of 68.2% in diagnosing GOR. With two reflux episodes observed in 12 (29.2%) patients, the sensitivity was 30% and specificity of 72.7%. Seven (17.1%) patients had three or more refluxes during the screening period giving a sensitivity of 20% and specificity of 90.9%.

Barium oesophagogram and ultrasound

When the results of both tests were combined to detect GOR in 38 patients, seven patients (18.4%) showed positive reflux on ultrasound and barium oesophagogram. In combination when both tests showed positive reflux, the sensitivity of the test was 21.4%, specificity of 90% and a positive predictive value of 80%. When a positive reflux is detected on barium oesophagogram, the specificity and positive predictive value increased to 100% when three or more refluxes were observed concurrently on ultrasound. These were present in three (7.9%) patients. Collapse/consolidation being the most commonest radiological abnormality was chosen as one of the predictors. The combination of chest radiograph with two positive tests for reflux produced a sensitivity of 10.7% and a positive predictive value of 75%. The presence of three or more reflux episodes from the ultrasound findings increased the specificity to 100%.

Discussion

Pulmonary manifestations are serious manifestations in gastro-esophageal reflux disease (GERD). In evaluating the significance of each symptoms to diagnose GOR, none of these symptoms were sensitive enough to be used as a clinical predictor. Although cough has a high positive predictive value, it is not specific being a frequent manifestation of chronic lung disease.

Table II
Predictive Validity of Respiratory Symptoms Evaluated for GOR

Symptoms	No (%) with Symptoms	Sensitivity (%)	Specificity (%)	Positive Predictive Value (%)	Negative Predictive Value (%)
Persistent wheeze	16 (36.3)	41.9	76.0	81.2	35.7
Persistent cough	22 (50.0)	51.6	53.8	72.7	31.8
Stridor	9 (20.4)	19.3	76.9	66.0	28.5
Apnoea/ALTE*	6 (13.6)	9.6	76.9	50.0	26.3
Choking	11 (25.8)	25.8	76.9	72.7	30.3
Vomiting and regurgitation	20 (45.4)	48.3	61.5	75.0	33.3
Haematemesis	1 (2.2)	3.2	1.0	1.0	30.2
Irritability	1 (2.2)	3.2	1.0	1.0	30.2
Seizure	4 (9.0)	9.6	9.2	75.0	30.0
Wheeze and cough	10 (22.7)	25.8	84.6	80.0	32.3
Wheeze and vomiting	6 (13.6)	16.1	92.3	83.3	31.6
Choking and wheeze	4 (9.1)	9.7	92.3	75.0	30.0
Choking and stridor	1 (2.3)	0	92.3	0	36.0
Vomiting and stridor	3 (6.8)	9.7	100.0	100	31.7

**ALTE: Acute life threatening episode*

Table III
Patterns of Radiological Changes on Chest Radiographs

X ray Changes	No (%)	Positive Reflux on pH Study	Negative Reflux on pH Study
Hyperinflation	5 (11.4)	4	1
Segmental/ lobar collapse/ consolidation	17 (38.6)	11	6
Hyperinflation+ collapse/ consolidation	8 (18.2)	5	3
Others	1 (2.2)	1	0
Normal	13 (29.5)	10	3

Cough may be caused by other than aspiration due to reflux such tracheo-oesophageal fistula and dysco-ordinate swallowing. Therefore it has to be taken in combination with other symptoms. Symptoms such as wheeze, vomiting, choking and stridor were the most specific predictors of GOR when any of these two symptoms are present at the same time. There are no previous studies that actually evaluate these clinical symptoms.

Chest radiograph is the most basic radiological investigation performed in patients with significant respiratory symptoms. It is not specific in diagnosing GOR but demonstrates lung changes resulted from aspiration. Collapse/consolidation is the commonest radiological findings particularly involving the right upper lobe. This may signify aspiration either from reflux gastric contents or from oral contents due to choking or dys-coordinate swallowing. This is not a specific sign but with a history to suggest reflux will support the evidence of GOR.

Hyperinflation is a specific radiological sign in predicting GOR in this study. Hyperinflation means there is airway obstruction resulting in air trapping which is normally seen in asthmatic patients. Absence of collapse/consolidation an chest radiographs support the evidence that besides direct aspiration, respiratory symptoms can be induced via reflex mechanism such as reflex bronchospasm and reflex laryngospam[3,4]. A normal chest radiograph does not exclude severe or significant

GOR. As in this study, 13 patients had normal chest radiographs of which 10 had significant GOR on pH study. GOR was demonstrated in 34.1% of patients by barium oesophagogram. This was similar to previous studies by Euler *et al*[1] and Berquist *et al*[2] who demonstrated GOR in 23.3% and 36.6% patients respectively. Barium oesophagogram is less valuable in diagnosing GOR. The reasons of its high false positives and negative results may be due to excessive crying during the procedure, excessive pressure on the abdomen, the use of head down position which is nearly guaranteed to produce reflux and the overzealous reading of small wisps of barium refluxes indicating significant reflux. The specificity of ultrasound improved when there are three or more refluxes during the screening period which is similarly reported by Riccabona *et al* who demonstrated 87.5% specificity. However absence of reflux does not rule out GOR. The reason for high false negative and low sensitivity of the test was due to short screening time where reflux may not occur during this period.

In summary, with the high prevalence (70.5%) among patients with respiratory symptoms GOR needs to be ruled out. The clinical predictors for GOR were identified as any of the two following symptoms i.e. wheeze, vomiting, choking and stridor. The presence of these symptoms should raised a high index of suspicion of GOR. There is no single test which is sensitive or specific enough to detect GOR and may not replace the utility of pH oesophageal monitoring. Therefore a combination of two tests are recommended. This study was able to demonstrate that the combination of two tests i.e. ultrasound and barium oesophagogram improved the specificity and positive predictive values of diagnosing GOR. This study has identified useful symptoms and procedures that may help clinicians to diagnose GOR. As a guide, in centres where pH are not available, clinical predictors in combination with two positive tests for reflux are recommended.

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