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Retrospective Study

The Prevalence of Gastro Esophageal Reflux in Cystic Fibrosis Patients in a Tertiary Care Center

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Abstract

Introduction: The Prevalence of Gastro esophageal reflux (GER) has reported to be around (63%) of Cystic fibrosis (CF) patients. It has long been suspected of exacerbating a variety of respiratory diseases.

Objectives: To identify the prevalence of GER in our CF patients, the type of the diagnostic tools that have been used to identify GER, and the type of medical or surgical intervention that have been used to treat GER.

Methodology: A retrospective chart review as part of the CF registry data from the period 1st January 1984- 1st June 2018. All confirmed CF the patients of all age group that have positive GER from their radiological investigations during their follow up period in CF clinic were reported, in addition to the medical and surgical interventions that were carried out.

Results: A total of 198 confirmed CF patients, underwent at least one diagnostic radiological study for GER. Ninety-two (46%) had positive GER and 106 (54) was negative for GER. A total of 101/198 patients (51%) who had cumulative positive GER from both groups (92 patients had positive GER from the first study and 9 patients from the initial negative group), had GER treatment and repeated radiological investigations until total resolution of their symptomatology and negative radiological studies. A total of 10/101 (10%) patients who had positive GER, required surgical intervention in the form of gastrostomy and Nissen-fundoplication to improve their weight gain and reduce GER at mean age of 3.2 (2.89) years. Two patients required a repeat second surgical intervention.

Conclusion: GER is a common complication of CF disease. Physician should routinely assess the symptomatology of the GER and its recurrence and institute medical treatment early to prevent lung damage. Surgical intervention may be needed in persistent GER.

Keywords: *Cystic Fibrosis; Gastroesophageal Reflux; CFTR; PH Monitoring*

Introduction

Cystic fibrosis (CF) is the most common lethal genetic disease in Caucasians, and currently affects about 30,000 individuals in the United States [1]. It is caused by a mutation in CF transmembrane conductance regulator gene (CFTR), where it is characterized by an

imbalance in chloride transport in multiple organs. Although airway obstruction, inflammation, and infection are usually the major cause of morbidity and mortality of CFTR dysfunction because they lead to respiratory failure, CFTR dysfunction affects the intestinal tract, pancreatic and hepatobiliary ducts in a similar way, leading to significant morbidity [2].

Most CF patients suffer from Gastroesophageal reflux (GER). It is the physiological phenomenon of an effortless retrograde flow of gastric contents into the esophagus [3].

Maqbool A., *et al*. 2017, found that the prevalence of increased esophageal acid exposure varies from 15 to 76% in infants, from 20 - 55% in children and up to 90% in adults with CF [3].

Blondeau K., *et al*. 2008, found that: the prevalence of increased acid GER in CF was estimated to be between 35 and 81%, from all CF patients who underwent reflux testing (n = 33), 21 had increased acid reflux (18 with high esophageal acid exposure and three with increased number of acid reflux events) [4].

Poddar., *et al*. 2018 reported that, GER is common in early infancy and has almost disappeared by one year of age. The continuation or development of regurgitation after 18 months of age suggests a pathological condition. Moreover, he found that during childhood, the prevalence of GERD increases slowly with age and becomes frequent in young adults. A cross-sectional observational study of 10,394 French children (0 - 17 years) estimated that 10% of all children have GER and 6.2% with GERD [5]. GER causing troublesome symptoms or complications (such as esophagitis or Barrett's esophagus) is referred to as gastroesophageal reflux disease (GERD) [3].

Lord RW., *et al*. 2016 reported an increased number of reflux episodes in 80% of the adult CF patients undergoing 24-hour observation using the PH-MII. Moreover, almost 60% increased 'high-risk' proximal reflux or supine reflux was noted on these patients [6].

Arash A., *et al*. 2010 reported that (63%) of CF patients in his study had GER symptoms and almost a quarter (24%) had frequent other symptoms) such as respiratory diseases [7].

Robinson N., *et al*. 2014 described a prevalence of 35 to 81% GER in CF patients. He described that for those CF patients that have a coexisting GER, they will have a more severe lung disease which affect the lung function and cause respiratory exacerbations. He described some of the predisposing factors to GER that lead to decreased LES pressure as: airway hyperinflation which results in depressed diaphragm and widened sterno-vertebral diameter, increased intra-abdominal pressure associated with chronic cough, delayed gastric emptying, high fat-diet, positional changes, medications taken by CF patients and high levels of cholecystokinin in patients diagnosed with pancreatic insufficiency [8].

Höhne S., *et al*. 2014 reported that in 11 of 12 CF patients found to have a pathologically low pressure of the lower oesophageal sphincter (LES) and concluded that the LES is not fully developed, which results in lower esophageal relaxations, that lead to retrograde flow of gastric contents into the esophagus or even aspiration into the lungs [9,10] For this reason, gastro esophageal reflux (GER) became prevalent in patients with (CF) and can play a role in the pathogenesis of respiratory disease [11,12].

Objectives of the Study

To obtain the prevalence of GER in CF patients who underwent radiological study and or PH- probe study.

Methodology

After obtaining the ethical approval, we retrospectively reviewed charts of 387 patients with cystic fibrosis of all age groups from the period of 1st January 1984 - 1st June 2018.

Cystic fibrosis was diagnosed on typical clinical picture of cough, sputum production and high sweat chloride test in two subsequent testing samples > 60 mmol/L by the Wescor quantitative method, USA. In the study, routine evaluation of all patients included: detailed medical and family history, physical examination, laboratory investigations and CFTR mutation testing [13].

Definitions: A patient with CF disease is defined as:

1. One who has a typical pulmonary manifestation and/or typical gastrointestinal manifestations (GI) and/or a history of cystic fibrosis in the immediate family in addition to sweat chloride concentration > 60 mmol/ liter.

2. Pathologic CFTR mutations on both alleles.

3. One who has a typical pulmonary and gastrointestinal manifestations and borderline or normal sweat chloride (CL) level (30 - 60 mmol/L), and or pathologic CFTR mutations on both alleles.

Inclusion criteria: All CF patients of all ages that had radiological studies from GER from the period 1st January 1984 - 1st June 2018.

How GER is diagnosed: GER was diagnosed based on the following studies.

Barium study: A barium swallow test is a special type of imaging test that uses barium and X-rays to create images of upper gastrointestinal (GI) tract [1] in a clinical trial study, comparing the efficacy of fluoroscopic detection of spontaneous and provoked gastroesophageal reflux compared with 24-hr monitoring of esophageal PH. Barium studies showed spontaneous reflux in 26% of subjects proved by PH measurements to have GER. The sensitivity of barium detection rose to 70%, with a specificity of 74% and positive productive [1].

The modified barium swallow (MBS) study is a video fluoroscopic evaluation of oropharyngeal swallow function Judgments of bolus flow through the esophagus were made in AP view during four swallows: (1) one-fourth of a graham cracker coated with 5 cc. barium paste (Varibar 40% w/v, EZ EM Bracco diagnostics Monroe Twp., NJ); (2) 13-mm barium tablet (E-Z-Disk 700 mg.); (3) one large (uncontrolled volume) patient administered swallow of barium contrast (E-Z-Paque 70% w/v) imaged passing the length of the esophagus and; (4) one large (uncontrolled volume) patient administered swallow of barium contrast imaged at the lower esophagus and assessed passing through the lower esophageal sphincter (LES). If there was a delay in bolus passage, brief views were obtained at 30 and 60s. If barium contrast did not clear at 60s, a sip of water was provided and results were recorded. See table 1 for the protocol [14].

Variable	Value	Number total 198 (100%)
Gender	Male	99 (50%)
	Female	99 (50%)
Region	E	72 (36.3%)
	W	35 (17.9%)
	C	47 (23.3%)
	N	23 (12.1%)
	S	21 (10.5%)
Patient status	Alive	131 (66.5%)
	Died	67 (33.5%)

Table 1: *Demographic data of cystic fibrosis patients (Total = 198 patients).*

Legend table 1

E= East; W= West; C= Center; N= North; S= South.

Barium swallow is an X-ray test for diagnosis of esophageal disorders such as achalasia, diverticula, dysphasia, gastroesophageal reflux disease (GERD) etc. This test gives a qualitative idea of how efficiently a bolus is transported through the esophagus. We have developed a technique by which we can analyze a barium swallow fluoroscopy and calculate the velocity and pressure distribution inside the esophagus. In this technique, we use a Convolutional Neural Network to perform segmentation of image sequences generated from a fluoroscopy and use these segmented images as input to a reduced-order model to calculate the velocity and pressure in the fluid inside the esophagus. We have also used this method along with High Resolution Manometry (HRM) to identify and estimate biomarkers such as wall-relaxation that occurs ahead of the peristalsis wave in the esophagus wall. This reduced-order model can run very fast, and hence can be used in clinical applications to add more quantitative information to the barium swallow test, thus resulting in better diagnosis of esophageal disorders [15].

Nuclear medicine scan in GER: GER scintigraphy is an important study in pediatric nuclear medicine. It is a sensitive, noninvasive, physiological technique to demonstrate GER and lung aspiration. It is easy to perform and does not require significant patient cooperation. some studies found the sensitivity of GER scintigraphy to be 60% - 90% and the specificity over 90% [16]. Nuclear medicine is a sensitive, noninvasive, physiological technique to demonstrate GER and lung aspiration. Previous studies showed that the sensitivity of GER scintigraphy to be 60% - 90% and the specificity over 90% [16]. The investigated group comprised of 76 children, aged 1 - 204 months (mean 74 months) with clinical signs and symptoms of GER. All of them underwent GUT scintigraphy, GUT scintigraphy confirmed reflux in 60/76 children (78.9%) [2].

PH-probe: Four-channel antimony probes are used. They are small (1.5 mm diameter), soft, pliable, inexpensive, durable, and have lower impedance than glass electrodes. The channels are spaced 3 to 8 cm apart to conform to pediatric and adult? esophageal lengths. The patient-worn, small, 500 gm esophageal pH ambulatory recorder-EpHAR-stores pH data sampled every 15 seconds from each of the four channels for 32 hours of reliable battery life. The recorder is carried in a pouch or placed at the bedside at night and stores pH samples with a resolution of 0.05 pH units [17]. In our study, the parameters of positive GER were:

1. Total number of reflux = > 100 for infants, and > 73 above infancy.

2. Percent time clearance = PH > 4.2% For infants and > 10% above infancy [17].

Management of patient with GER: All Cf patient presented with symptoms and signs of GER (vomiting, substernal pain, heart pain shocking or coughing with feeding) were send for barium study (Ba study) or nuclear medicine (NM study) according to the discretion of the physician and the agreement of the family. Once GER is confirmed in either one of the studies the patient is given anti-reflux medication as omeprazole (losec) for 6 months, then the radiological study was repeated (study # 2). If ger is positive the treatment will continue for another 6 months and another study will be repeated 6 months later and the same process will continue until complete resolution of GER. Same patient may continue to have symptom despite negative radiological study and will be treated accordingly until the radiological study is negative or PH monitoring study is normal. Surgical intervention with Nissen-fundoplication was done with patients underwent treatment for 1 - 2 years of medical treatment between failed to improve symptomatically or radiologically.

CFTR identification: As described before in a previous study [18].

Ethical considerations: After obtaining the ethical approval by the research advisory committee. The Declaration of Helsinki and good clinical practice guidelines were followed. Data collection and data entry were supervised by the principal investigator. All data needed were obtained by retrospective chart review. All data were stored in pediatrics research unit, accessed only by the principle investigator and the assigned Clinical Research Coordinator. The entire patient's information kept strictly confidential. Each patient was given a study number, and all patients' data were entered in to the designated data sheet (EXCEL) without any patient's identification. The department of Biostatistics Epidemiology and Scientific Computing (BESC) carried out statistical analysis of the data.

Statistical method: The T-Test was used to calculate the continuous variables, median, mean, and standard deviation. All values were expressed in mean ± standard deviation (SD) and results were presented at a level of significance of $p < 0.05$.

Results

A total of 430 CF patients aged 3 months to 37 with a median age (interquartile range) was 10.2 months (4.4 months to 5.7 years) at diagnosis and 9.7 (5.4-16.5) years at follow up. Ninety-nine (50%) were males and 99 (50%) were females from the different regions from Riyadh, Saudi Arabia (Table 1). The Eastern province constituted 72 (36.3%) from the total CF population (Table 1).

One hundred and ninety-eight patients of the total 430 patients (46%) patients underwent at least one diagnostic study due to their symptoms with either a barium swallow or a nuclear medicine scan to evaluate the presence or absence of gastro esophageal reflux (GER) (Figure 1). The mean age at the first radiological study was 4.7 (5.6) years (a range of 0.3 - 28.93 years) and the second radiological study at a mean of 7.3 (6.07) years (a range of 0.5 - 19.06 years) and the third radiological study at a mean of 9.2 (4.14) years (a range of 6.29 - 12.15 years). Out of the 198 patients, 92 (46%) patients had positive GER, and the remaining 106 (54%) patients were negative. Out of the 92 patients, 45 (49%) patients, underwent a second diagnostic study. Nineteen out of the 45 patients (42%) were positive for GER for the second time. Eighteen from the 19 patients (95%) had negative GER, and only one patient underwent numerous subsequent diagnostic tests, all of which were negative for GER (Figure 1).

Seven out 26 patients (27%) who had negative second study required two subsequent studies due to persistent symptoms until complete resolution (Figure 1).

On the other hand, 106/198 (54%) patients who were negative for GER in the first study, 23/106 (21%) of them required a second study, 9/23 (39%) of them were positive for GER. Out of the 9 patients 6 (67%) patients did two subsequent studies and were provided with medical treatment until complete resolution of GER symptoms (Figure 1).

A total of 101/198 patients (51%) who had cumulative positive GER from both initial study of positive and negative groups (92 patients had positive GER from the first study and 9 patients from the second study of the initial negative group) had GER treatment and had repeated radiological study and medical management until total resolution of their symptomatology and negative radiological investigation (Figure 1 and table 2).

A total of 65 patients through the whole study period had PH-study with impedance monitoring for 24 hours, 20 of 65 (30.7% were positive according to the parameters that were mentioned above) and 45 (69.3%) were negative. The Median bolus clearance time was > 44 seconds, and All Reflux percent times were > 1.4% and DeMeester score > 14.7.

The degree of GER was assessed in 101 patients by both radiological studies, and the interpretation was: mild in 20 (19%), moderate in 22 (21%) and severe in 60 (60%).

Metoclopramide was prescribed for 14/101(14%) for vomiting, Ranitidine (Zantac) was prescribed in earlier period before its withdrawal from the market for 15 (15%) of patients and Omeprazole (Losec) was prescribed for the remaining 72/101 (71%) of patients.

A total of 10/101 (10.1%) patients who had positive GER, required surgical intervention in the form of gastrostomy and Nissen fundoplication for improvement of weight gain and persistent GER at mean age of 3.2 (2.89) years, with age ranged from 3 months-18 years. Two patients required a second surgical intervention due to the failure of the first surgery.

The overall prevalence of GER in 101/198 patients who underwent GER study is considered to be 51%.

Discussion

Gastroesophageal reflux is a primary phenomenon in cystic fibrosis patients and is more prevalent than in general population [19]. Lung aspirations of duodenogastric fluid are an underestimated risk factor for the lung disease progression. Advanced lung disease additionally increases gastroesophageal reflux risk [19]. Many symptoms and signs of cystic fibrosis are overlapping with those of gastroesophageal reflux disease and are not a prognostic factor for its presence or severity level. Despite a lot of evidence, controversies regarding gastroesophageal reflux disease diagnosis and treatment in cystic fibrosis patients still exist. One of diagnostic challenges is lung aspiration detection [19]. Proton pump inhibitors are the mainstay of the treatment employed in half of all patients. Antireflux operation in selected patients probably slows the decline of lung function [19].

In our study, a total of 101/198 patients (51%) who had cumulative positive GER from both initial study of positive and negative groups (92 patients had positive GER from the first study and 9 patients from the second study of the initial negative group) had GER treatment and had repeated radiological study and medical management until total resolution of their symptomatology and negative radiological investigation (Figure 1 and table 2). The prevalence of 51% is considered higher than most of the studies that were reviewed. This increase may be interpreted as to the dependence on radiological study as the initial evaluation and not to PH-probe and impedance measurement due to parental hesitancy to do this type of test.

Study #	Frequency (%)	GER (%)		Outcome (%)		
		Yes	No	Improvement	No change	Deterioration
1st study	198	92 (46.5%)	106 (53.5%)	-	-	-
2nd study	68/198 (34.3%)	28 (41.2%)	40 (58.8%)	26 (38.2%)	33 (48.5%)	9 (13.2%)
3rd study	18/68 (26.5%)	4 (22.2%)	14 (77.8%)	6 (33.3%)	9 (50%)	3 (16.7%)
4th study	6/18 (33.3%0	1 (16.7%)	5 (83.3%)	0	6	0
5th study	1/6 (16.7%)	1	0	0	0	1

Table 2: *Outcomes of radiological investigations (Barium and Nuclear scan studies) for GER (Total = 198 patients).*

Legend Table (2)		
Key	**Explanation**	
Outcome	Outcome of current study compared to previous study	
Improvement	Testing negative for GERD in the current study after testing positive for GERD in the previous study	
No change	Same result for GERD as previous study	
Deterioration	Testing positive for GERD in the current study after testing negative for GERD in the previous study	
Percentage %	Frequency %	% From total number of patients who underwent previous study
	GER %	% From total number of patients who underwent current study
	Outcome %	% From total number of patients who underwent current study
1st	First	
2nd	Second	
3rd	Third	
4th	Forth	
5th	Fifth	

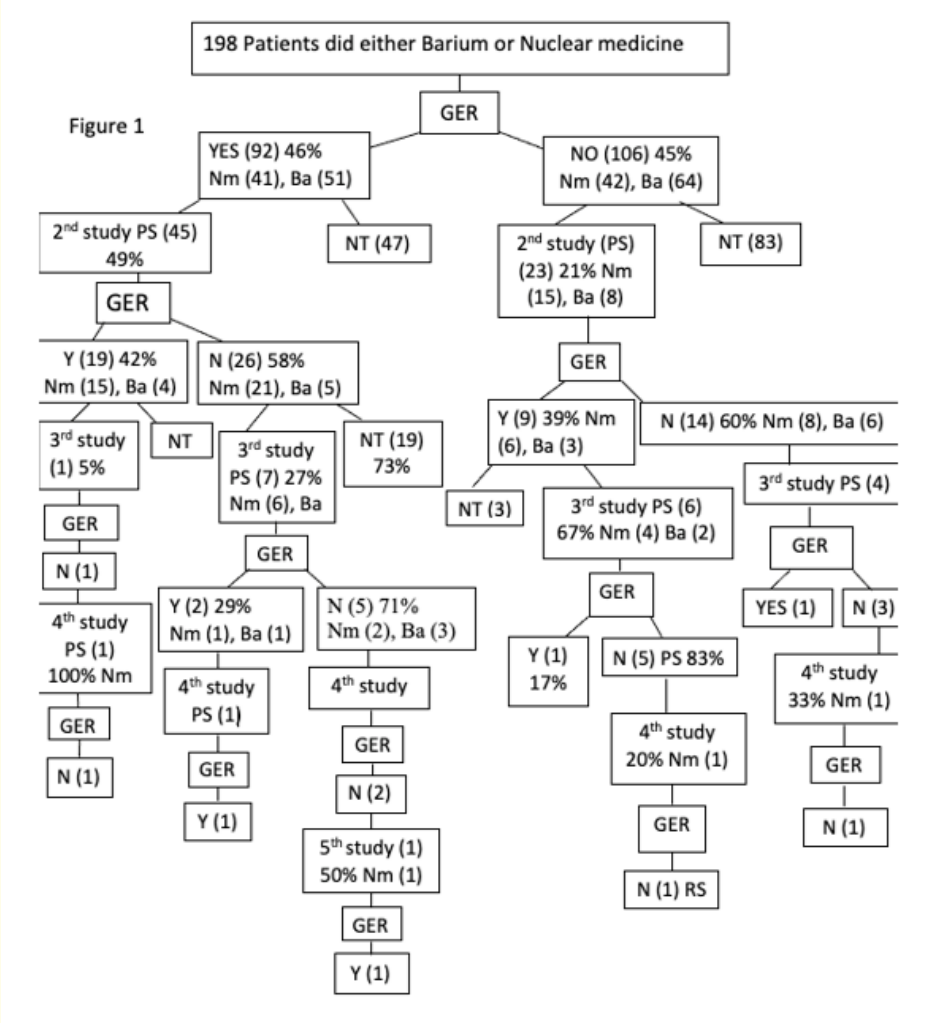

Figure 1: *Radiological investigations for GER management (total 198 patients).*

Legend figure 1

Ba: Barium Swallow Study; Nm: Nuclear Medicine Study; GER: Gastroesophageal Reflux; Y: Yes for GER; N: Negative for GER; PS: Persistent Symptoms; NT: Nothing Done.

To assess Gastroesophageal reflux in cystic fibrosis across the age spectrum, Woodley., *et al*. [20] carried out a study to assess the effect of GER on PH, he searched the esophageal pH-multichannel intraluminal impedance monitoring database for tracings belonging to CF patients ≥ 2 years old without prior fundoplication and not taking anti-reflux medications immediately prior (within 7 days) and during the study. Tracings were retrospectively analyzed; Impedance and pH variables were evaluated with respect to age and pulmonary function. His results showed that of the 28 patients that were enrolled; 16 children (3.1 - 17.7 years) and 12 adults (18.2 - 48.9 years). Among pH probe parameters, correlation analysis showed DeMeester score (P = 0.011) and number of acid reflux events lasting > 5 minutes (P = 0.047) to be significantly correlated with age and that both age and increased acid exposure are associated with reduced BI in the distal

esophagus. Pulmonary function (percent predicted forced expiratory volume in one minute; $ppFEV_1$) was negatively correlated with age (r = −0.494, P = 0.0007). The interaction of age and $ppFEV_1$ and any of the reflux parameters, however, was not significant (P > 0.05); the strongest evidence for an interaction was found for the number of acid reflux events reaching the proximal esophagus, but this interaction still did not reach statistical significance (P = 0.070). This pilot study supports the need for esophageal assessment and treatment of GER as standard components of clinical care for an aging CF population [20].

In our study, a total of 65 patients through the whole study period had PH-study with impedance monitoring for 24 hours, 20 of 65 (30.7% were positive according to the parameters that were mentioned above) and 45 (69.3%) were negative. The Median bolus clearance time was > 44 seconds, and All Reflux percent times were > 1.4% and DeMeester score > 14.7. These parameters are considered moderate to severe in its degree, but most of the time, the study was carried out as confirmatory or follow-up studies rather than initial diagnostic study.

Antireflux surgery (ARS) is offered to a selected CF cohort with refractory GERD. Published data for children with CF are limited and heterogeneous in terms of GERD diagnosis and outcomes following ARS. Jessica., *et al*. [21] carried a systematic literature-based search using various online databases according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines. The number of GERD cases in pediatric CF cohorts who underwent diagnostic investigation(s) was recorded. Data on postoperative complications and outcomes (including symptoms, lung function, and nutritional status) following ARS were analyzed. He found that: Ten articles (n ¼ 289 patients) met the defined inclusion criteria (51% male; age range, 0.5 month - 36 years). The overall incidence of GERD was 46% (range, 19 - 81%), derived from seven studies (n ¼ 212 patients). Four publications (n ¼ 82 patients) reported on ARS due to uncontrolled GERD. All ARSs were Nissen fundoplication (majority with gastrostomy placement). Major postoperative complications occurred in 15 (18%) patients, two required redo-ARS. Median follow-up time was 2 years (range, 3 months - 6 years); 59% showed symptom improvement, and pulmonary exacerbations and decline in lung function were reduced. Nutritional status mainly improved in milder CF cases. There were no deaths related to ARS. Her conclusion was that: Approximately half of pediatric CF patients have GERD. However, ARS has shown to slow the deterioration of lung function in CF [21].

In our study, a total of 10/101 (10.1%) patients who had positive GER, required surgical intervention in the form of gastrostomy and Nissen-fundoplication for improvement of weight gain and persistent GER at mean age of 3.2 (2.89) years, with age ranged from 3 months-18 years. Two patients required a second surgical intervention due to the failure of the first surgery. There was no registered complication, but the weight gain was not dramatic due to delay in its application due to parental refusal of early placement and nutritional intervention and the fear of it as a stigma of final stage of the disease or death.

Chen., *et al*. [22] studied the predictive effect of positive reflux-cough correlation on the resolution of reflux-related chronic cough after anti-reflux surgery. It was a 5 years' retrospective review. Logistic regression analysis was used to determine the independent predictors on the cure of chronic cough. His results showed: Seventy-nine patients were included in this study, among which chronic cough was cured in 47 (59.5%) and significantly improved in 10 (12.7%) patients. Present of typical symptoms (odds ratio = 6.435,95% confidence interval [CI] = 1.427 - 29.032, p = 0.015) and number of Reflux episodes (impedance) ≥ 73 (odds ratio = 0.306, 95% confidence interval [CI] = 0.107 - 0.874, p = 0.027) were significantly associated with the cure of chronic cough. His conclusions were that: laparoscopic Nissen-fundoplicaiton is effective for the management of reflux-related chronic cough, particularly with the present of typical symptoms [22]. Our study did not evaluate the role of surgery on cough frequency, and further study is needed to evaluate such correlation.

Button BM., *et al*. [23] studied the effect of physiotherapy on 20 patients with comparing (standard physiotherapy SPT) to (modified physiotherapy MPT). He found that: Gastroesophageal reflux is increased in cystic fibrosis and it is possible that postural drainage techniques may exacerbate reflux, potentially resulting in aspiration and further impairment of pulmonary function. The number of reflux episodes per hour, but not their duration, was significantly increased during SPT compared with MPT. Therefore, SPT, but not MPT, was associated with a significant increase in gastroesophageal reflux in infants with cystic fibrosis [20].

The policy that is followed in our CF population is to apply STP in patients < 4 - 5 years of age and MPT by using Acapella for breathing technique or another alternative at > 5 year of age. Our study did not evaluate the role of SPT or MPT in our CF GER prevalence.

The correlation of GER and pulmonary function test or CFTR mutations were not evaluated in our study, further evaluation of such factors is encouraged [18].

Conclusion

GER is a common complication of CF disease. Physician should routinely assess the symptomatology of the GER and its recurrence and institute medical treatment to prevent lung damage. Surgical intervention may be needed in persistent GER.

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