ORIGINAL ARTICLE

Frequency distribution of gastro esophageal reflux disease in inhalation injury: A historical cohort study

Ashraf Karbasi[1], Rasoul Aliannejad[1,2], Mostafa Ghanei[1], Mehran Noory Sanamy[3], Farshid Alaeddini[1], Ali Amini Harandi[3]

[1]Chemical Injuries Research Center, Baqiyatallah University of Medical Sciences, [2]Department of Pulmonary, Shariati Hospital, Tehran University of Medical Sciences, [3]Department of Neurology, Shahid Behashti University of Medical Sciences, Tehran, Iran

Background: There is no data on the prevalence and the association of gastro esophageal reflux disease (GERD) with toxic fume inhalation. Therefore, we aimed to evaluate the frequency distribution of GERD symptoms among the individuals with mild respiratory disorder due to the past history of toxic fume exposure to sulfur mustard (SM). **Materials and Methods:** In a historical cohort study, subjects were randomly selected from 7000 patients in a database of all those who had a history of previous exposure to a single high dose of SM gas during war. The control group was randomly selected from adjacent neighbors of the patients, and two healthy male subjects were chosen per patient. In this study, we used the validated Persian translation of Mayo Gastroesophageal Reflux Questionnaire to assess the frequency distribution of reflux disease. **Results:** Relative frequency of GERD symptoms, was found to be significantly higher in the inhalation injury patients with an odds ratio of 8.30 (95% confidence interval [CI]: 4.73-14.55), and after adjustment for cigarette smoking, tea consumption, age, and body mass index, aspirin and chronic cough the odds ratio was found to be 4.41 (95% CI: 1.61-12.07). **Conclusion:** The most important finding of our study was the major GERD symptoms (heartburn and/or acid regurgitation once or more per week) among the individuals with the past history of exposure to SM toxic gas is substantially higher (4.4-fold) than normal populations.

Key words: Frequency, gastro esophageal reflux disease, inhalation injury, mustard gas

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INTRODUCTION

Gastro esophageal reflux disease (GERD) is a common chronic disorder.[1] It is defined as a condition that develops when the reflux of stomach contents causes troublesome symptoms and/or complications. The prevalence in the Western world generally ranges from 10% to 20% whereas, in Asia the prevalence is reported to be <5%.[2]

Patients with a variety of chronic respiratory diseases, including asthma, cystic fibrosis, and idiopathic pulmonary fibrosis,[3] have a higher prevalence of reflux disease when compared to the general population. However, all of these studies except on asthma were done on the advanced pulmonary disorder.

Above all, frequency of esophagitis diagnosed with both endoscopic and pathologic criteria is significantly higher in patients with sulfur mustard (SM) induced chronic cough.[4] In another uncontrolled study de la Hoz *et al.* investigated the presence of GERD among former World Trade Center (WTC) rescue and recovery workers and found that the presence of reflux disease in those patients was related to degree of pulmonary function abnormalities.[5]

There is no knowledge about the prevalence and the association of GERD with toxic fume inhalation.

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Address for correspondence: Dr. Rasoul Aliannejad, Shariati Hospital, Pulmonary Department, Tehran University of Medical Sciences, Tehran, Iran. E-mail: aliannejad@tums.ac.ir

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Therefore, we conducted a historical cohort study was conducted for evaluation of the frequency distribution of GERD symptoms among individuals with mild respiratory disorder due to past history of toxic fume exposure to SM and a possible association between them.

MATERIALS AND METHODS

Patient selection

In this historical cohort study, subjects were randomly selected from 7000 patients in a database of all those who had a history of previous exposure to a single high dose of SM gas during Iran-Iraq conflict in 1988. The inclusion criteria were documented exposure to mustard gas, normal respiratory function or mild respiratory impairment documented by the Global Initiative for Chronic Obstructive Lung Disease (GOLD) criteria.[6]

All the subjects were male. Patients with moderate to severe respiratory impairment (documented by the GOLD criteria), history of hospital admission due to respiratory disease, asthma, known history of GERD prior to mustard exposure, known esophageal disease (cancer, achalasia, stricture), active peptic ulcer disease, diabetes, history of open abdominal or open chest surgery along with addicts, and patients treated with corticosteroids were excluded.

Control group

The control group was randomly selected from adjacent neighbors of the patients, and two healthy male subjects were chosen per patient. They denied having any respiratory symptoms (dyspnea, cough) or a previous diagnosis of chronic obstructive pulmonary disease (COPD) or asthma. Exclusion criteria for this group were similar to the patients group.

All the study population was residents of Tehran (capital of Iran) and had lived in this city for more than 20 years. They were all interviewed by a single interviewer (general practitioner) in their own home, and the Gastroesophageal Reflux Questionnaire (GERQ) was filled out for those satisfying the eligibility criteria.

In this study, we used the validated Persian translation of Mayo GERQ[7] was used to assess the frequency distribution of GERD symptoms. The "modified Persian Mayo GERQ" contains 79 questions and asks the subject to rate how often 16 common symptoms occur and how bothersome they are. Briefly, it covers demographics (gender, age, marital status, weight, height, and educational level), and major (acid regurgitation [AR], heartburn [HB], dysphagia, and chest pain) and minor (see variables and definitions) GERD symptoms in the past 3 and 12 months. The first question for each symptom acts as a branch point and subjects who answer "no" proceed to the next symptom. The next two questions for each symptom refer to the frequency and severity of the symptom. Symptom frequency was measured on a scale of 1-6 in the following categories: None in the past year, one to ten times in the past year, about once a month, about once a week, several times a week, or daily. The severity of symptoms was classified as mild, moderate, severe, and very severe. The remainder of the questionnaire assessed subjects' demographic data, smoking history, use of over-the-counter antacids, and prescription anti-reflux medications. Generally, the questionnaires were completed in <20 min.

Definitions

HB and AR were defined as "two major GERD symptoms." HB, AR, dysphagia, and chest pain as "four major GERD symptoms;" and cough, anorexia, belching, hoarseness, nausea, foreign body sensation in the throat, and food regurgitation as "potential minor GERD symptoms." GERD was defined as the presence of at least one of two major GERD symptoms (HB or AR) during the past 12 months. Those having daily or weekly GERD were considered to have "frequent GERD," and those with less frequent symptoms as having "infrequent GERD."

The study was approved by the Ethics Committee of the chemical injuries research center. Informed consent was obtained from all patients before the questionnaire was administered.

Statistical analysis

Data are shown as a mean ± standard deviation (SD). SPSS 15.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis. Chi-square test was used for categorical variables and independent Student's *t*-tests and Mann–Whitney U-test were employed for continuous variables. For the final analysis, logistic regression (LR) model was used to eliminate the effect of confounding factors. Results were reanalyzed using forward LR model. Hosmer–Lemeshow index, the coefficient of determination were calculated for a fitness model. $P < 0.05$ was considered as statistically significant.

RESULTS

Clinical and demographic characteristics are summarized in Table 1. The study population was composed of male subjects only, and the two groups were matched for age. Body mass index (BMI) was slightly higher in the inhalation injury group (mean BMI [±SD], 27.2 ± 4.8 vs. 25.9 ± 3.7, $P = 0.01$).

The pack-year data were obtained by multiplying years of smoking by a number of packs of cigarettes used per day. None of the study population was alcoholic, and coffee consumption was negligible.

Table 2 demonstrates the higher frequency distribution of reflux symptoms in patients and controls during the last 3 and 12 months.

Frequency distribution of GERD symptoms was found to be significantly higher in the inhalation injury patients with an odds ratio of 8.30 (95% confidence interval [CI]: 4.73-14.55), and after adjustment for cigarette smoking, tea consumption, age and BMI, aspirin usage, and chronic cough the odds ratio was found to be 4.41 (95% CI: 1.61-12.07) which is shown in Table 3. Hosmer–Lemeshow index, coefficient of determination and the area under the receiver operating characteristic (ROC) curve were calculated for fitness model that showed goodness of fit for LR models and high discriminative power (Hosmer–Lemeshow goodness of fit = 6.85, $P = 0.55$; Nagelkerke $R^2 = 0.40$; Area under the ROC curve = 0.84). In forward LR model, only the two variables in the model remained significant, as well.

Table 1. Baseline characteristics of the study population

	Inhalation injury patients	Normal population	*P* value
Number	120	240	–
Age (years)	45.4±7.4	44.8±8.1	0.4
Height	172.8±6.5	171.3±6.8	0.9
Weight	81±15	77.5±12.1	0.03
Body mass index	27.2±4.8	25.9±3.7	0.01
Smoking	0.193±0.396	0.256±0.437	0.002
Tea	0.916±0.277	0.944±0.231	<0.001
Aspirin	0.23±0.47	0.07±0.25	<0.001
Non-steroidal anti-inflammatory drugs	0.05±0.22	0.03±0.19	0.49

All subjects were male; None of the study population was alcoholic and coffee consumption was negligible; Independent Student's *t*-tests were employed for continuous variables

Table 2. Multivariate adjusted model for GERD symptoms in those with and without inhalation

	Inhalation injury patients (%)	Normal population	*P* value
Heart burn (HB)			
More than once a week (Last 3 months)	40.8	6.7	0.001
Acid regurgitation (AR)			
More than once a week (Last 3 months)	51.7	8.8	0.001
Any HB or AR (Last 3 months)	59.2	11.7	0.001
Dysphagia (Last 12 months)	25	0.8	0.001
Food regurgitation (Last 12 months)	8.7	9.5	0.8
Nausea (Last 12 months)	5.2	5.7	0.8
Hoarseness (Last 12 months)	72.9	20.3	0.001
Globus sensation (Last 12 months)	6.1	7.2	0.6

Chi-square test was used for categorical variables

Table 3. Effect of GERD confounding factor between and within groups

variable	Odds ratio	Std.Err	*P* value	95 % Confidence limit	
Between groups	4.419396	2.267212	0.004*	1.616906	12.07928
Smoking	1.233674	0.412124	0.53	0.640983	2.374404
Tea	0.876239	0.503482	0.818	0.284137	2.702205
Age	1.009505	0.059505	0.872	0.899363	1.133136
Body mass index	0.974991	0.047397	0.602	0.886383	1.072456
Aspirin	1.246842	0.929108	0.767	0.289416	5.371556
Chronic cough	2.8091	1.473433	0.049*	1.004833	7.853089

Dependent variable is GERD; Logistic regression model was used to eliminate the effect of confounding factors; *Statistically significant

DISCUSSION

The most important finding of our study was that major GERD symptom (HB and/or AR once or more per week) among the individuals with the past history of exposure to SM toxic gas is substantially higher (4.4-fold) than normal populations and relative frequency of heartburn, and AR was 40.8% and 51.7%. In our study, the relative frequency of major reflux symptoms, including heartburn and AR was 6.7% and 8.8%, respectively among the normal population.

Although our patients were randomly selected from those who did not have any major respiratory symptoms, some had a prescription history of inhaled β2-adrenergic agonist and/or anticholinergic medications. This data were registered in our database and analyzed using the conditional LR test, in which no correlation was found between reflux symptoms and inhalators agents' usage ($P = 0.4$).

It is speculated that prevalence of GERD might increase in asthma and COPD. The collective prevalence values indicate that the prevalence of symptoms of GERD among the individuals with asthma is higher (1.6-fold) than the control group. However, none of the studies reporting the prevalence of GERD in asthma was population-based and only three of these studies considered whether the severity of asthma had an impact on the presence, severity, or frequency of GERD symptoms. According to these studies prevalence of GERD symptoms was 30% in mild, 46% in moderate, and 70% in severe asthma.[8]

The prevalence of GERD in COPD patients was reported with different results. The prevalence of GERD is reported about five-fold more than the general population among advanced COPD patients,[3] but a recent study indicated that there was no difference between the prevalence of GERD symptom in COPD and control groups.[9] However,

most of these studies were done on severe COPD, and they were also done in secondary or tertiary referral center.[3,10-12]

The relative frequency of GERD symptoms in our patients was significantly higher than other respiratory disorders. Also, our study was done on individuals with normal to mild respiratory impairment (according to GOLD criteria). Contrary to the previous statement that there is a trend toward higher prevalence of GERD symptoms in patients with more severe airways obstruction,[11] in this study the higher prevalence of GERD symptoms was not associated with the presence of significant respiratory impairment.

The hypothesis for the association between SM exposure and GERD can be through toxic inhalation injury, systemic absorption of SM from the skin and/or mustard related pulmonary disorders. Whether this effect is related with the possible predisposing direct effect of this toxic agent on esophageal epithelium such as the effect of extract of cigarette smoking is not known de la Hoz *et al*. have also noticed that GERD is associated with early arrival at the WTC site, and they have proposed that toxicant inhalation may have triggered some upper digestive inflammation which has led to reflux disease, consequently GERD and airway or pulmonary disease may have a bidirectional association.[5]

The most important question that should be clarified in future is whether there is a possible mechanism for chemical agent (SM) exposure and GERD relationship.

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Conflicts of interest

There are no conflicts of interest.

AUTHOR'S CONTRIBUTION

AK: Study conception and design, Critical revision, Data gathering. RA: Study conception and design, Critical revision, Data gathering. MGh: Study conception and design, Critical revision, Data gathering. MNS Study conception and design, Data gathering. FA: Study conception and design, Analysis and interpretation of data. AAH: Analysis and interpretation of data, Critical revision, Drafting of manuscript.

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