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Evaluation of chronic cough in chemical chronic bronchitis patients

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Abstract

Background: Coughing is one of the chronic respiratory symptoms of patients exposed to sulfur mustard (SM) used against Iranian combatants and civilians by Iraq during the Iran–Iraq war, between 1983 and 1989. This study carried out on SM exposed patients who referred to our clinic because of exacerbation of chronic cough.

Method: Fifty male SM injured patient in the age range of 21–79 years, all of them having chronic bronchitis and were suffering from chronic cough (>3 weeks) were evaluated. After history taking and performing physical examination our diagnostic evaluation included chest X-ray, pulmonary function test (PFT), para nasal computerized tomography, esophageal endoscopy and fiber optic bronchoscopy.

Results: Apart from having chronic bronchitis as a constant disease in all patients, the other main causative factors behind chronic cough were bronchospasm, post-nasal drip syndrome (PNDS), and gastro esophageal reflux disease (GERD), which accounted for 66%, 46% and 44% of chronic cough of the patients, respectively. A single cause for chronic cough was found in 4 patients (8%), 2 causes in 17 patients (34%), 3 causes in 23 patients (46%) and 4 causes in 6 patients (12%).

Conclusion: Since a high majority of the patients had more than a single cause for chronic cough, multiplicity of causes of chronic cough in a patient is indicative for evaluation of possible exposure to chemical fumes, especially SM. Because of high prevalence of chronic bronchitis (100%) and bronchospasm (66%) among our study group we conclude that they should be considered at first, before assessment of other causes.

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Keywords: Chronic cough; Bronchitis; Sulfur mustard

1. Introduction

Chronic cough and sputum production are manifestations of chronic bronchitis among Iranians who has been exposed to sulfur mustard (SM) in Iran–Iraq war (Security Council, 1986; Emad, 1997). Sulfur mustard is capable of producing severe chemical injuries in primarily three major organs: skin, eyes and lungs. It is well documented that inhalation of sulfur mustard causes injury of the respiratory system which is manifested by chest pain, cough, sore throat and hoarseness (Winterniz, 1919; Khateri et al., 2003). Lethal exposures result in death from respiratory failure, secondary pneumonia,

and occasional hemorrhagic pulmonary edema (Rosemond et al., 2003).

Persistent cough has prompted a great number of patients to seek medical services. According to previous studies, this problem interferes with ordinary activities of 14–23% of non-smoking adult population who suffer from it (Irwin and Curley, 1991; Palombini et al., 1999). The etiology of chronic cough was determined in several studies and the five most important causative factors were bronchospasm, post-nasal drip syndrome (PNDS), gastro esophageal reflux disease (GERD), bronchiectasis and tracheobronchial collapse. Coughing was due to single cause in 38.5% and multiple causes in 61.5% (Di Pede et al., 1991). Although previous studies evaluated the etiology of chronic cough in the general population, the main objective of this study

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was to evaluate chronic cough causes in chemical exposed patients who were all suffering from chronic bronchitis.

2. Materials and methods

According to the reports, approximately 34,000 Iranian people, both civilian and military, have been exposed to CWA during the Iran–Iraq war from 1983 to 1988 (Khateri et al., 2003). This cross-sectional descriptive study which was carried out from 2000 to 2002 (about 15 years after the exposure), evaluated patients who were suffering from chronic cough and because of exacerbation of this problem, were referred to the Baqiyatallah out patient clinic. Fifty male patients were eligible for inclusion.

2.1. Inclusion criteria

- (1) Documented chemical exposure by the veteran (Janbazan) organization which is the official center for compensation of war disabled victims. Exposure in this study was defined as a single, high-dose exposure to a chemical agent that causes transient or permanent disability in exposed people.
- (2) Medical records documenting care received for chemical exposure. According to the records, all injured victims were transferred to local military hospitals, where the type of chemical agents was determined based on signs and symptoms and also by special kits. The physicians treated the patients using standard protocols determined by military health services. Patients with signs and symptoms compatible with nerve agent exposure were treated with atropine, diazepam, and oxime; those who presented with blisters on their skin were treated with supportive care and sodium thiosulfate.
- (3) A productive cough on most days for 3 months in two consecutive years (Medical Research Council, 1965).

2.2. Exclusion criteria

- (1) Smokers.
- (2) Those who did not continue diagnostic process.
- (3) Heart failure.
- (4) Lung cancer.
- (5) Family history or prior diagnosis of asthma.

3. Diagnostic procedures

We assessed all patients prospectively in the following method (Irwin et al., 1990):

- For all patients a medical history taking and physical examination were performed, concentrating on the anatomical locations of afferent limb known to contain receptor sites for the cough reflex (e.g., the nose, the nasopharynx, the lungs).

- Chest radiography was ordered for all patients.
- If findings of medical history and physical examination suggested PNDS, X-ray and CT scan of the sinus was obtained.
- If chest radiography showed abnormalities compatible with infection, expectorated sputum studies were performed.
- If medical history, physical examination and the chest radiogram did not show any abnormality, the responsiveness of pulmonary function to a bronchodilator was evaluated to determine bronchospasm. Pulmonary function studies consisted of spirometry before and after the inhalation of salbutamol, were performed in all patients. Positive response was demonstrated if force expiratory volume in the first second (FEV1) has been improved with more than 12% after inhalation of salbutamol.
- If, at this stage, we could not discover the etiology of chronic cough, gastro esophageal endoscopy and biopsy was ordered to evaluate the presence of GERD.
- If, despite aforementioned steps cough persisted, uncommon causes such as bronchiectasis, tumor and so on, were considered and evaluated with bronchoscopy.

4. Diagnostic criteria

Prospective criteria were established for the presumptive diagnoses of PNDS, bronchospasm, GERD, chronic bronchitis and bronchiectasis as the etiologies of chronic cough in adult patients.

PNDS was considered in patients who expressed the sensation of something dripping down into their throat, nasal discharge, the frequent need to clear their throats, physical examination revealing mucoid or mucopurulent secretions or a cobblestone appearance of the mucosa. Rhinosinusitis was considered as potential cause of PNDS when the sinus roentgenograms (such as X-ray or CT scan) demonstrated more than 6 mm of the mucosal thickening, air fluid levels, opacification of any of the sinuses (Pratter et al., 1999), association of the cough with nasal congestion and a purulent discharge as revealed by examination of the nasal cavities or posterior oropharynx in the absence of abnormal CT scan findings.

Bronchospasm was considered when patients complained of episodic wheezing, shortness of breath and cough, and were heard to wheeze; reversible air flow obstruction was demonstrated with PFT (improvement of FEV1 more than 12% after inhalation of salbutamol (Murray and Nadel, 2000; Johnson and Osborn, 1991)). The diagnosis of bronchospasm was not made in any patient who had experienced an obvious respiratory tract infection within 2 months before examination.

GERD was identified with the presence of heartburn, sour taste in mouth and specific pathologic change for GERD in esophageal endoscopic biopsy (Ismail-Beigi et al., 1970). Bronchiectasis was considered when chest radiogram demon-

strated an increase in size or loss of definition of markings in specific segmental areas of the lung, honey combing; signs of compensatory hyperinflation, or if patient had purulent-appearing or blood-stained sputum expectoration (Fraser et al., 1990).

5. End points

A favorable response to a specific therapy was considered diagnostic of the primary cause if cough attenuated. The end point for treatment was cough resolution, defined as a patient report of complete absence of cough for two consecutive weeks.

Step 1. Patients with sinus roentgenograms consistent with sinusitis were treated with twice daily oxymetazoline hydrochloride nasal spray for 3 days, nasal corticosteroids twice daily, antihistamine-decongestant twice daily, and antibiotics for as long as 6 weeks. If cough still persisted, a computed tomographic study of the sinuses was obtained. If substantial abnormalities were present, the patient was referred for an otolaryngologic evaluation and possible sinus surgery.

Step 2. Abnormal chest X-ray findings compatible with infection was treated with appropriate antibiotics.

Step 3. Patients who were still coughing after previous trial were next evaluated for bronchospasm. Patients with positive response were treated for 1 week with an inhaled beta₂-agonist (salbutamol) two puffs four times a day via metered-dose inhaler. If cough persisted, prednisone therapy (1 mg/kg body weight per day (maximum, 60 mg/day)) was added to the salbutamol for a week. An oral beta₂-agonist or theophylline was substituted for the inhaled salbutamol if a patient reported marked cough in response to inhaled salbutamol.

Step 4. If the therapy with salbutamol had negative response, GERD was considered as the other cause chronic cough. If confirmed with history taking, physical examination and gastroesophageal endoscopy, a 2-week regimen of high-dose proton pump inhibitor therapy (such as omeprazole, 40 mg bid) along with antireflux measures were prescribed. If the patient has responded, we continued the proton pump inhibitor at a high dose for 2 months and then began to slowly taper the dose. If the patient has not responded to the proton pump inhibitor therapy, 24-h ambulatory esophageal pH testing (while the patient was receiving medication) was recommended to determine the adequacy of acid suppression and the possible need for more medication.

Step 5. Having diagnosed uncommon causes of chronic cough through fiber optic bronchoscopy, a specific therapy was considered accordingly.

6. Final diagnostic criteria

No cause of cough was considered definitive until treatment for that cause had been effective (that is, was associated

with marked improvement or resolution). When therapy for only one diagnosis resolved the cough, that diagnosis was considered to be the sole cause of cough. When therapy for a diagnosis affected marked improvement short of resolution, that diagnosis was considered to be one of the causes of cough and treatment was continued while additional diagnoses were investigated.

7. Results

According to the mentioned criteria, 50 patients were enrolled in the study: all of them were male and their mean age was 40 ± 5 years. The average time lapse from SM exposure was 18 ± 2 years in our study group. Thirty-six percent (18 patients) expressed hemoptysis, 46% (23 patients) had PNDS, 66% (33 patients) had bronchospasm and 44% (22 patients) had GERD. The data of the number of causes of chronic cough and the frequency of each combination of causes are shown in Table 1. Only four patients (8%) had a single causative factor (chronic bronchitis) for chronic cough.

8. Discussion

Chronic cough is one of the most common symptoms prompting outpatient medical visits. The prevalence of chronic cough depends on smoking status, and has been estimated at 5–40%, depending on the group studied. Chronic bronchitis, usually due to cigarette smoking, is thought to be the most common overall cause of chronic cough in general population (Di Pede et al., 1991).

As demonstrated in previous studies, in the absence of use of angiotensin-converting enzyme (ACE) inhibitors, the pathogenic triad of PNDS, asthma, and GERD have consistently accounted for 90–100% of cases of chronic cough among immunocompetent adults (Irwin et al., 1981, 1990, 1998; Smyrniotis et al., 1998; Pratter et al., 1993).

In the present study, although non-smokers, all patients were suffering from chronic bronchitis. Likewise, our study showed that aforementioned causes contribute to the main

Table 1
Percentage and distribution of causative factors of chronic cough in study group

Number of causes	Cause combinations	Percentage	Total (%)
1	CB	8	8
2	CB + BS	18	34
	CB + GERD	10	
	CB + PNDS	6	
3	CB + BS + GERD	20.5	46
	CB + BS + PNDS	15.5	
	CB + GERD + PNDS	10	
4	CB + BS + PNDS + GERD	12	12

CB: chronic bronchitis, BS: bronchospasm, GERD: gastro esophageal reflux disease, PNDS: post-nasal discharge syndrome.

etiologies of persistence and exacerbation of chronic cough in SM induced chronic bronchitis patients.

According to some studies, bronchospasm is detected in most patients with bronchial asthma, in a half with exogenous allergic alveolitis, in more than a third with chronic bronchitis and pulmonary tuberculosis, and in a fifth with pulmonary sarcoidosis (Nefedov et al., 2001). Moreover, it has been proved that bronchospasm plays an important role in development of bronchial obstruction in chronic bronchitis patients (Nefedov and Shergina, 2000). In the present study, we observed 66% bronchospasm among SM induced chronic bronchitis patients, indicating it as the second most common contributor of chronic cough. Then, it should be diagnosed and treated at first.

We also concluded that GERD makes up the next cause of chronic cough among our study group. This finding is compatible with previous prospective studies in which GERD (solely or along with other diseases) was mentioned as one of the main causes of chronic cough, ranging from 7.7% to 40% (Mello et al., 1996). Unawareness from this issue can put the patient in a vicious cycle, because coughing provokes GERD and then, inadequate treatment of these coexisting causes can perpetuate cough-reflux cycle (Irwin et al., 1998). It was seen that conservative antireflux measures along with H₂-antagonists and/or prokinetic drugs, resulted in the resolution of cough in 70–100% of adult patients (Irwin et al., 1989). We suggest above-mentioned measures to be prescribed because of the high prevalence of GERD in exacerbation occasions in all chronic cough patients with symptoms of GERD.

According to some reports, in 18–62% of patients referred to medical clinics, there are two, and in up to 42% there are three causes of chronic cough (Irwin et al., 1981, 1990; Smyrniotis et al., 1995).

Awareness of the fact that chronic cough can be simultaneously due to more than one condition is important for accurate diagnosis and successful treatment of cough (French et al., 1998). The importance of this fact, especially in mustard gas exposed patients, increases when we compare the results of our study with unexposed (normal population) individuals. Accordingly, more than 90% of patients in our study had combination of causes of chronic cough.

Therefore, we concluded that despite the presence of known causes of chronic cough such as chronic bronchitis in SM exposed patients, more evaluations should be done on any SM induced chronic bronchitis patient for other causes of chronic cough, especially in uncontrolled or recent exacerbations of chronic cough. Furthermore, since multiplicity of causes in mustard gas exposed patients is considerably higher than normal population we suggest assessment for possible exposure to chemical fumes when face patients presented with chronic cough due to several causative factors. As indicated in our previous study (Ghanei et al., 2004) this conclusion can especially help us to consider sub-clinical exposure to SM among those had history of presence in contaminated battle fields and later developed late complications.

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