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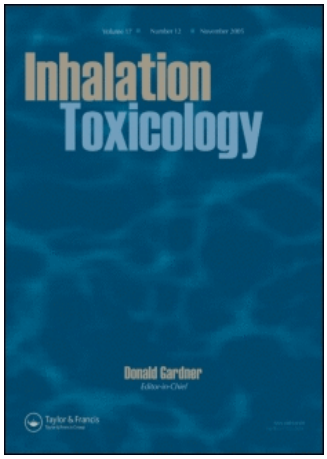

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Sinus CT Scan Findings in Patients with Chronic Cough Following Sulfur Mustard Inhalation: A Case-Control Study

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Sinusitis is one of the most common causes of chronic cough, which is the most common manifestation among patients exposed to sulfur mustard (SM). We conducted our study on exposed victims to SM with chronic cough for evaluation of probable sinus abnormality. In a case-control study, among referred patients for evaluation of persistent chronic cough, 39 patients with previous and 35 patients without previous history of exposure to SM underwent paranasal sinus computed tomography (CT) scans (Somatom CR CT scanner) in coronal planes. A well-designed standard pro forma was used for reporting sinus CT abnormalities. Data was analyzed with chi-square and Fisher exact test. Except one, all obtained CT scans findings showed some abnormalities. Mucosal abnormality was detected in 30 chemical-exposed cases (CEs) (76.9%), and 8 cases were categorized as severe types. In general, mucosal thickening in right (left) frontal, sphenoid, and maxillary sinus were observed in 12.8% (7.7), 5.1% (7.7), and 25.6% (30.8) of CEs, respectively; these proportions were 11.4% (11.4), 2.9% (2.9), and 45.6% (60) in non-chemical-exposed cases (NEs), respectively. Air fluid level in the right (left) frontal sinus was 10.3% (7.7) and in the right (left) maxillary sinus was 10.3% (15.4) in CEs; it was 2.9%(0) and 20%(20) in NEs for these locations, respectively. There were no statistically significant differences between findings of two groups ($p > .05$). Also, comparison of related data to osteomeatal complex obstruction, bulla ethmoidalis, haller cell, agger nasi, and pneumatized crista galli were not significant ($p > .05$). Thus; various types of sinus abnormalities were highly prevalent in both CEs and NEs with chronic chough and there was no specific pattern. Consequently, current approaches to chronic cough just based on conventional etiologies in this setting can lead to delay in diagnosis and mismanagement.

Many gases, vapors, or particles found in occupational and/or environmental settings can act as irritants following inhalation. They are characterized by stimulation from the mucosa of nasal passages to bronchoalveolar airspaces (Castranova et al., 2002; Littorin et al., 2002; Collins, 2002). The initial contact area of inhaled toxins with the human body is the nasal mucosa. Upon irritation, nasal symptoms may occur that are well known from common viral infections of the airway (Klimek et al., 2002).

Sulfur mustard (SM, chemically 2,2′-dichlorodiethyl sulfide), a potent toxic fume, is very lipophilic and can therefore penetrate epithelial tissues easily. Therefore, mustards can cause severe systemic intoxication beside their pronounced local damaging capacity (Kehe & Szinicz, 2005). Some evidence strongly proposes a bidirectional effect of SM: directly via inhalation, and indirectly from recirculation. Whole-body autographic studies with ^{35}S-labeled SM have shown that elevated radioactivity was detected in the nasal region after percutaneous or intravenous administration (Clemedson et al., 1963).

Thousands of Iranian people were exposed to chemical warfare agents (CWA), especially SM, during the Iran–Iraq war from 1983 to 1988 (Security Council, 1986). The eyes, nasal mucosa, throat, pulmonary tract, and skin were most commonly affected sites. After a symptom-free period, irritation of nasal mucosa, hoarseness, sneezing, and coughing develop. Moderate exposure results in lacrimation, rhinorrhea, loss of smell and taste, and mucus discharge from nose and throat. Severe exposure causes edema in upper and lower airways with ulcerations and necroses (Kehe et al., 2005). According to this evidence, in the acute phase SM has close contact with nasal passages and upper airway mucosa. More to the point, following inhalation, in the chronic phase, chronic cough and sputum production were manifestations of chronic bronchitis among these patients (Emad, 1997; Ghanei et al., 2005). The etiology of chronic cough

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was determined in several studies. Five most important causes are bronchospasm, postnasal drip syndrome, gastroesophageal reflux disease, bronchiectasis, and tracheobronchial collapse. Also, postnasal discharge is one of the most common cause of chronic cough resulting from chronic sinusitis.

Taken together we hypothesized that sinus abnormalities in SM-exposed patients who suffer from chronic cough could be common due to toxic effects of SM. We conducted our study on patients with chronic cough who had documented exposure to SM for evaluation of probable sinus abnormalities in addition to conventional etiologies.

METHOD AND MATERIAL

Based on a descriptive case-control study that has been done on patients with documented chemical warfare agents (CWA) exposure, 39 cases with chronic cough were collected randomly. All cases were referred to our respiratory clinic for evaluation of their persistent chronic cough. Inclusion criteria were: (1) cough symptoms of at least 3 wk duration (Weinberger, 2005); (2) exposure to chemical warfare documented by military health services; and (3) medical records of the patients documenting the care received for chemical exposure. Exposure in this study was defined as a single, high-dose exposure to the chemical agent that caused transient or permanent disabilities in exposed people. Patients with recent upper-respiratory-tract infection history or previous history of nasotracheal intubation or specific history of paranasal sinus surgery or maxillofacial trauma were excluded. Written informed consent in accordance with protocols approved by the appropriate institutional review board was obtained from each patient.

All cases were referred from respiratory disease clinic to clinical imaging section for evaluation of chronic cough and evaluation of prevalence of sinonasal abnormalities. Computed tomography (CT) scan images were obtained on a Somatom CR CT scanner (SOMATOM Sensation 16; Siemens, Forchheim, Germany). Contiguous thin slices were taken with the patient lying in the prone position without gantry tilt in the coronal plane. Noncontrast paranasal CT scans were obtained in coronal planes for evaluation symptoms of sinus disease. A well-designed standard pro forma was used for reporting sinus CT abnormalities (Elahi et al., 1996). All films were reported in blinded fashion by a single experienced radiologist. In addition, after official reading by the radiologist, all films were reviewed by an otolaryngologist, and both reports were then compared and differences were noted and reassessed. Commentary was made as to the visualization, pneumatization, and opacification of the ethmoid, maxillary, sphenoid and frontal sinuses, including mucoperiostial thickening and opacification of paranasal sinuses (frontal/ethmoid/sphenoid/maxillary), maxillary cyst and turbinate anomaly (paradoxically curved/turbinate hypertrophy/conch bullosa), septal deviation, prominent ethmoid bulla haller cell, agger nasi cell, and lateral or medial deviation of the uncinated process. Mucosal disease if present was subdivided to be scored as mild, moderate, or severe. Mild mucosal disease was defined as mucosal thickening < 2 mm, while severe mucosal disease was considered to be presented with thickening >5 mm. The term *cyst* represented an umbrella term for either mucocele or retention cyst, requiring the radiologist to identify them. A section provided for the middle turbinate, bulla ethmoidalis, haller cell, aggar nasi, and uncinate process to be checked off whenever present and/or prominent, with or without osteomeatal complex obstruction, which is addressed as a separate area. Similarly, there was room for comment on a low-lying fovea ethmoidalis and cribiform plate, as well as for dehiscence of the lamina papyracea and vulnerability of either the carotid canal or the optic nerve. The anterior and middle ethmoidal air cells are considered collectively under the heading of anterior ethmoid sinus. Most of the parameters included required only a check in the appropriate box, ensuring minimal description wherever possible.

Parameters just mentioned were compared with control consecutive coronal CT scans performed on 35 patients with chronic cough without history of exposure to CWA. They were clinically suspicious for sinus abnormalities according to signs and symptoms. The control group underwent CT scans with the same method and device mentioned for exposed patients.

The obtained results were analyzed by Fisher exact and χ^2-test. The calculations were performed with the SPSS software program version 11 (SPSS, Inc., Chicago). A p value of less than .05 was considered to be statistically significant.

RESULTS

The patients ranged in age from 17 to 70 yr. The mean age was 37.9 ± 7.6 yr in CEs and it was 36.5 ± 10.4 yr for NEs. From all obtained CT scans, 1 was normal and 73 had abnormalities. Mucosal abnormality was detected in 30 CE cases (76.9%) and 8 (20.5%) cases were severe; among them, in 5 cases 1 sinus (12.8%), in 1 case 2 sinuses (2.6%), in 1 case 3 sinuses (2.6%), and in 1 case 4 sinuses (2.6%) were abnormal. There was not dehiscence of the lamina papyracea on vulnerability of either the carotid canal or the optic nerve.

No differences were found in various types of sinus abnormalities between the CEs and NEs groups. The details of the CT scan findings in CE and NE cases are shown in Table 1.

DISCUSSION

According to our results, sinus abnormalities in the CE patients were as highly prevalent as in the NEs who had chronic cough due to sinus abnormalities alone. Also, these abnormalities had no specific macroscopic patterns in exposed patients comparison to control group. Histopathological characters in this setting may be notably different with special features, but this was not our aim in this study.

Interestingly, our findings reveal that various types of sinus abnormalities had the same frequency distribution between both groups of patients. These abnormalities are well known as the main predictor for chronic cough. Although the etiology of

TABLE 1
Comparison of different types of sinus abnormality between SM-exposed patients and control group with chronic cough

Types of sinus abnormality	Percentage		Significance
	Exposed	Nonexposed	
Mucosal thickening RT (LF)			
Frontal	12.8 (7.7)	11.4 (11.4)	$p = .1$
Maxillary	25.6 (30.8)	45.6 (60)	$p = .1$
Sphenoid	5.1 (7.7)	2.9 (2.9)	$p = .1$
Ethmoid			
Anterior	15.4 (15.4)	20 (20)	$p = .1(0.1)$
Posterior	10.3 (5.1)	17.1 (17.1)	
Air–fluid level RT (LF)			
Sphenoid	2.6 (5.1)	0 (2.9)	$p = .3(0.6)$
Frontal	10.3 (7.7)	2.9 (0)	$p = .2(0.1)$
Ethmoid	0 (2.6)	0 (2.9)	— (0.9)
Maxillary	10.3 (15.4)	20 (20)	$p = .2(0.6)$
Others RT (LF)			
Bulla ethmoidalis	15.4 (7.7)	25.7 (22.9)	$p = .2(0.6)$
Haller cell	2.6 (2.6)	8.6 (2.9)	$p = .2(0.9)$
Agger nasi	2.6 (5.1)	5.7 (0)	$p = .4(0.1)$
Uncinate process	0 (0)	2 (0)	$p = .1(-)$
Maxillary cyst	7.7 (15.4)	11.4 (8.6)	$p = 0.5(0.3)$
Crista galli pneumatized	5.1	8.6	$p = .5$
Complete (partial) OMC obstruction			
RT	5.1 (10.3)	14.3 (8.6)	
LF	10.3 (7.7)	14.3 (14.3)	$p = .5(0.7)$
Bilateral	17.9 (5.1)	17.1 (8.6)	

Note. OMC, osteomeatal complex; RT, right; LF, left.

chronic cough was determined previously (Di Pede et al., 1996), our study for the first time made clear the role of sinus abnormalities as an additional cause to the conventional etiologies mentioned before. Consequently, this unknown source may be ignored in the presence of common etiologies. Hence persistence of cough can occur because of mismanagement and delay in diagnosis and lack of appropriate treatment in this setting.

Many of the animal studies of toxicity from inhaled SM were conducted during World War I. They showed that inhaled SM vapor produced destruction of the epithelium of the respiratory tract. Apparently, much of the vapor is removed in the upper respiratory tract: The nasal, laryngeal, and tracheobronchial regions appear to be the most severely affected (Papirmeister et al., 1991). In rabbits, inhalation of SM produced damage that was particularly prominent in the upper respiratory tract, including the nasal passages, pharynx, larynx, trachea, and large bronchi (Warthin & Weller, 1919). The damage increased with increasing exposure concentrations. Low levels of exposure caused congestion of these areas without hemorrhage. However, two studies conducted during World War I suggested that low-level exposure or survivable exposures in dogs and rabbits might produce scar tissue following small ulcerations in the trachea and larynx, leading to contractions of these areas (Warthin & Weller, 1919; Winternitz, 1919).

Furthermore, there is some evidence supporting direct and indirect effects of SM on the upper respiratory airway of human in which sinus mucosa could not make an exception. In the absence of follow-up studies that directly address the question, however, this can still be pursued by examining indirect evidence from studies of compounds that might behave similarly. The inhalation of SM causes acute damage to the respiratory tract, but the symptoms of exposure are not immediate and develop over a period of several days. Damage to the respiratory tract involves acute edema (swelling), inflammation, and destruction of the airway epithelial lining. Depending on the dose, the destruction can be mild to severe. Severe damage includes destruction of the epithelium with subsequent formation of pseudomembranes (such as those formed in diphtheria infections), which may slough off and obstruct the airway, resulting in death (Pechura & Rall, 1993).

Indirect evidence, based on a review of the relationships between acute and chronic effects caused by other substances, suggested the likelihood of long-term respiratory effects in the absence of acute-phase symptoms. These effects may not

necessarily be linked to the presence of the early respiratory response in the acute phase. However, if acute exposure could lead to an alteration in individual risk factors, then it is possible that the magnitudes of the observed acute and chronic responses would be appeared unrelated. Thus, there is insufficient evidence to conclude that long-term respiratory responses occur only in cases where an earlier acute response has been documented (Pechura & Rall, 1993). The long-term changes can occur by independent mechanisms.

Since chronic cough is almost always a current symptom in these patients, it is unfortunate that the evaluation of patients without cough was not possible. Also, radiological patterns and histories before exposure were not available.

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