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RESEARCH ARTICLE

Long-term health status 20 years after sulfur mustard exposure

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Abstract

To describe the long-term health status of Sardasht civilians 20 years after sulfur mustard exposure, a historical cohort study was carried out in Sardasht (Iran) that included 372 exposed and 128 unexposed civilians. Their symptoms, diagnoses, drug use, and general health were compared. The most common complaints were about the respiratory system (93.5%), eyes (52%), skin (94.7%), and anxiety and depression (69.2%). Respiratory (42.5%), skin (75.5%), ophthalmic (19.6%), and mental (62.7%) diseases were diagnosed by specialists and they were more common in the exposed group than the control group ($P < 0.001$). Most of the exposed group had used drugs (70.6%), which was more than control group (42.8%). It seems that exposure to sulfur mustard caused a lot of health problems in Sardasht. Identifying the pathophysiology of these problems can help them more, but more investigation is needed.

Keywords: *Sardasht-Iran Cohort Study (SICS); sulfur mustard; health status*

Introduction

Mustard gas is one of the weapons that were widely used by the Iraqi army in the Iraq-Iran war (1981–1988) (United Nations Security Council, 1988). The civilians of Sardasht were targeted by mustard gas bombs in 1987 (Hashemian et al., 2006). In addition to acute extensive multi-organ problems, there are suggestions that long-term adverse health effects may also have resulted from the exposure to mustard gas (Balali-Mood and Hefazi, 2006; Ghanei et al., 2004; Hashemian et al., 2006). Various complaints and clinical presentations of the surviving people seeking medical care, and review of the literature, support such concerns, even though no systematic scientific evidence has been available. Several studies have reported on the health status of Iranian civilian chemical victims, including that by Ghanei et al. (2003), which indicated that common chronic problems in the survivors of Sardasht involved the respiratory system. Also, Attaran et al. confirmed the involvement of sulfur mustard in inducing obstructive pulmonary diseases in the Iranian victims (Attaran et al., 2006). To respond to the long-term health considerations

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among the victims of sulfur mustard gas, a comprehensive clinical and molecular study was established (Ghazanfari et al., 2009).

This study is a part of a large survey evaluating the health status of Sardasht civilians 20 years after mustard gas exposure, considering different aspects of general health. The purpose of this study was to extend and update the research on the health status of mustard victims, in particular an ordinary population of a town, not a special military group, 20 years after exposure. The nature and extent of symptoms and physically determined clinical diagnosis were assessed in the present study.

Materials and methods

A comprehensive historical cohort study was established in Sardasht, Iran, 20 years after sulfur mustard exposure, as the Sardasht-Iran Cohort Study (SICS). The details of study design and methods have been reported recently (Ghazanfari et al., 2009). In brief, 500 participants in this study were recruited from the male citizens of Sardasht (exposed) and Rabat (control). Both towns have the same geographical situations and weather. Further, both populations are Kurdish peoples with similar religion, culture, language, and nutritional habits. The age range covered by the study was 20 to 60 years. The entire exposed group had their history of exposure to sulfur mustard proven by medical records. Those who had history of systemic diseases before the exposure were excluded from the study. There was no significant difference in terms of age, body mass index (BMI), marital status, and smoking status between the control and exposed groups. The research protocol was approved by the Board of Research Ethics in the Janbazan Medical and Engineering Research Center (JMERC) and Shahed University. A written informed consent was obtained from all the subjects participating in the study. All the participants were evaluated at baseline for socio-demographic information, medical and family history, medications used over the last six months, anthropometric measurements, resting blood pressure, heart rate, and any symptoms or sign of diseases. More than 30 physical symptoms were included in the intake patient history questionnaire completed for each participant; then the symptoms were categorized into 11 main groups based on the related organs. Clinical examination findings were analyzed for both primary and secondary diagnoses among general ICD-9 medical condition categories. Percentages were generated for primary diagnoses independent of any secondary diagnoses codes. Data concerning exposure were evaluated and compared with the non-exposed group.

Statistical analysis

BMI and age were presented as mean ± standard deviation and compared with *t* test between study groups. Other variables were presented as frequency (percentage) and comparison between groups was done by chi-square test. Analysis was done with SPSS 13 (SPSS Inc, Chicago, IL). *P* values less than 0.05 were considered significant.

Results

Demographic characteristics of all participants, including 372 exposed and 128 non-exposed people, are shown in Table 1. As stated, there were no significant differences between the two groups in terms of age, marital status, or BMI. However, the exposed group had higher education and employment compared to the control group.

Table 1. Demographic Characteristics of Study Groups.

		Control	Exposed	*P* Value
Age (Mean ± SD)		42 ± 10	44 ± 11	0.262
BMI (Mean ± SD)		25.8 ± 4.0	26.3 ± 3.9	0.293
Age	Lower 50	92 (71.9%)	244 (66.5%)	0.261
	Upper 50	36 (28.1%)	123 (33.5%)	
Marital status	Single	11(8.6%)	33 (9.0%)	0.892
	Married	117 (91.4%)	334 (91.0%)	
Education	Lower diploma	9 (77.3%)	214 (58.3%)	<0.001
	Diploma and up	29 (22.7%)	153 (41.7%)	
Occupation	Occupied	73 (57%)	223 (60.8%)	<0.001
	Student	0 (.0%)	8 (2.2%)	
	Unemployed	42 (32.8%)	88 (24.0%)	
	Retired	1 (.8%)	29 (7.9%)	
	Unknown	12 (9.4%)	19 (5.2%)	

All the participants were asked about their symptoms at the present time. A large number in the exposed group reported currently experiencing at least one symptom (90.7%), and most reported more than one symptom (83%). All the symptoms of each organ were categorized in one main group and reported. The most common complaints were about the respiratory system, eyes, and skin. Anxiety and depression were common mental state problems (Table 2). The physician global assessment of general health is shown in Table 3. Considering the physicians' assessment, 79.3% of the unexposed group had good general health status, whereas, 47.4% of the exposed group were evaluated as being in good status. Physician-based clinical diagnoses are shown in Table 4 and are reported by ICD-9 general medical condition categories. Among them, the three most primary diagnoses were mental, respiratory, and skin diseases. Depression and anxiety were the most common psychological problems.

Medication in the last six months was substantially more frequent in the exposed group. Most of the exposed group had used at least one kind of drug (70.6%) in the last six months, which was substantially more than the control group (42.8%). The most frequently used medications and the number of drugs used by all participants are shown in Tables 5 and 6. The severely exposed people after the attack were hospitalized. The mean duration of hospitalization was 12.2 ± 8.4 days. Eight participants were dispatched abroad for more treatment. In the acute phase, they had mostly ophthalmic, skin, and pulmonary injuries. Sustainability of these symptoms over 20 years in participants who were hospitalized after exposure shows pulmonary symptoms remained more problematic. Wound scars were the cause of most of the various skin manifestations; ocular problems were less common than during the acute phase, but some of them were disabling problems (Table 7).

Table 2. Physical Symptoms Reported by Participants.

Symptoms	Control	Exposed	*P* Value
Weight change	2 (1.6%)	67 (18.3%)	<0.001
Headache	31 (24.2%)	184 (50.1%)	<0.001
ENT	8 (6.3%)	203 (55.3%)	<0.001
Pulmonary	83 (65.9%)	345 (93.5%)	<0.001
Gastrointestinal	14 (10.9%)	233 (63.5%)	<0.001
Urogenital	2 (1.6%)	151 (41.1%)	<0.001
Cardiovascular	3 (2.3%)	35 (9.5%)	0.015
Musculoskeletal	63 (49.2%)	254 (69.2%)	<0.001
Mental	3 (2.3%)	151 (41.1%)	<0.001
Skin	81 (63.3%)	338 (94.7%)	<0.001
Ophthalmic	48 (37.5%)	192 (52%)	<0.001
Without any symptoms	78 (60.9%)	34 (9.3%)	<0.001

Table 3. Physician Global Assessment of General Health Status of Study Population.

General health status	Control	Exposed	*P* Value
Good	104 (81.3%)	174(47.4%)	<0.0001
Moderate	24 (18.7%)	183(49.9%)	
Fair to poor	0 (0.0%)	10(2.7%)	

Table 4. The Number of Participants Diagnosed with a General Medical Condition.

	Control	Exposed	*P* Value
Musculoskeletal	12 (9.4%)	103 (28.1%)	<0.001
Ophthalmic	9 (7.1%)	72 (19.6%)	0.001
Skin/subcutaneous	71 (55.5%)	277 (75.5%)	<0.001
Respiratory system	39 (39.5%)	156 (42.5%)	0.016
Mental disorders	56 (43.8%)	230 (62.7%)	<0.001
Circulatory system	4 (3.1%)	77 (21.0%)	<0.001
Endocrine	43 (33.6%)	126 (23.2%)	0.879
Infectious/parasitic	4 (3.1%)	13 (13.9%)	0.823
Neoplasm	0 (0.0%)	1 (0.3%)	0.741

Table 5. Medication Used in the Last 6 Months.

Drug Type	Control	Exposed
Pulmonary	14 (10.9%)	142 (38.7%)
Antibiotic	14 (10.9%)	136 (37.1%)
Psychiatric	17 (13.3%)	111 (30.2%)
NSAIDs & Topical	8 (6.3%)	95 (25.9%)
Cardiovascular	4 (3.1%)	77 (21.0%)
Corticosteroid	10 (7.8%)	36 (9.8%)
Digestive	1 (0.8%)	25 (6.8%)
Supplement	2 (1.6%)	17 (4.6%)
Antihistamine	2 (1.6%)	16 (4.4%)
Other	8 (6.2%)	29 (7.9%)

Table 6. The Number of Drugs Used in the Last 6 Months.

Drug Count	Control	Exposed
0	86 (67.2%)	108 (29.4%)
1	20 (15.6%)	78 (21.3%)
2	8 (6.3%)	56 (15.3%)
3	10 (7.8%)	44 (12.0%)
≥4	4 (3.1%)	81 (22.1%)

$P < 0.001$

Table 7. Sustainability of Symptoms.

		At Exposure	After 20 Years
Ophthalmic	With problem	141 (83.9%)	53 (31.5%)
	Without problem	27 (16.1%)	115 (68.5%)
Skin	With problem	138 (82.1%)	122 (72.6%)
	Without problem	30 (17.9%)	46 (27.4%)
Pulmonary	With problem	64 (38.1%)	61 (36.3%)
	Without problem	104 (61.9%)	107 (63.7%)

Discussion

Few programs anywhere in the world are specialized to deal with the unique medical problems of victims of chemical attacks. Moreover, the substantial pool of such patients in Iran makes the country a logical venue for the development of a large-scale approach to this problem. An attack on unprotected people of a city with different demographic structures from a combat theater causes some distinctive large-scale health problems, which are incomparable with any other place. In addition, the people need special financial and scientific resources.

As shown in Table 2, there are substantially much more diverse complaints in exposed individuals. The patients who had more severe injuries after the exposure are still experiencing a greater variety of symptoms. In our results there is a disproportionate amount of subjective symptoms and objective signs. Several additional lines of evidence suggest that many patients with symptoms in fact have anxiety disorders, because of the mystery of the long-term impact of mustard gas on their health. Similar to other studies, depression and anxiety are more common findings in exposed group (Hashemian et al., 2006). The presenting symptoms (fatigue, headache, sleep disturbances, etc.) were more common in the exposed group. Even less common symptoms, such as dyspnea and chest pain, were more present in this group, although there is no clear physical finding to explain all of the symptoms revealed in the participants' physical examinations.

It is clear that the symptomatic individuals seek more medical services. Moreover, it has been shown that patients with mood and anxiety disorders often seek medical care (Kroenke et al., 1994; Narrow et al., 1993; Regier et al., 1978); on the other hand, physicians ignoring this point frequently fail to properly diagnose these treatable conditions (Linn and Yeager, 1984; Schulberg and Burns, 1988). This may be the reason for the high proportion of drugs prescribed only to relieve symptoms. In most of the somatic problems the diagnoses could not be based on the symptoms, because it is inversely proportional to the degree of complexity of evaluation, whereas the likelihood of psychological diagnoses is directly proportional to the level of evaluation to which patients are subject.

For the populations in which there is a concern regarding a mystery illness or an exposure-related disease, the importance of a multidisciplinary approach and a thorough diagnostic process is magnified, as Roy proposed (Roy et al., 1998). A careful history can guide the diagnostic evaluation. Then a complete physical examination is necessary, and finally paraclinical tests, if indicated, would be added. One strength of our study is this point, specifically that we carried out a multidisciplinary approach with fixed special physicians for all the stages of assessment to prevent different interpretations.

Rankings of diagnostic rates for all of the study groups suggest a clinically similar image of the exposed group compared to the control group, but the former has higher rates. As both towns were exposed to high-intensity conventional warfare throughout the war, this may be due to the effect of the massive stressors, but only Sardasht was exposed to chemical weapons. The most frequent primary diagnoses in the present study were mental, respiratory, and skin diseases. Our results confirmed the findings of the study by Hashemian et al., which showed that exposure to chemical warfare was an extremely traumatic event with long-lasting adverse consequences on mental health (Hashemian et al., 2006). Physician global assessment of eyes, skin, and lung health status revealed more severe complications in the exposed group. As other studies have already shown, pulmonary dysfunction is the most common complication and related chronic symptoms cause much more trouble for highly exposed groups (Balali-Mode et al., 2005; Emad and Rezaian, 1997; Ghanei et al., 2003; Khateri et al., 2003). Eyes had more acute reactions, but most of them recovered with time. Mustard gas causes chronic and delayed destructive lesions in the ocular surface and cornea, leading to progressive visual deterioration and ocular irritation (Javadi et al., 2005 and Ghasemi et al., 2008).

The scars of skin lesions remain for life and thus they have been utilized as a major indicator of mustard exposure (Ghanei et al., 2003). The most common lesions are eczema, xerosis, cherry angioma, hyperpigmentation and mustard scar (Moin et al., 2009). Finally, the pathophysiologic features of delayed consequences of mustard gas are not clearly identified. There is no laboratory test or biomarker that helps us in diagnosis and in planning proper treatment and follow up of complicated exposed people. On the other hand, there is no clear method to discriminate sulfur mustard–induced complication or other causes.

In conclusion, we suggest more research on basic and molecular mechanisms due to clinical complications of sulfur mustard. In another part of this study we are going to define more details of clinical consequence of this gas in different organs and evaluate the molecular mechanisms involving these clinical problems.

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