

## Prevalence of Asthma in Children of Chemical Warfare Victims

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### Abstract

**Objective:** Exposure of DNA to sulfur mustard gas may increase the inheritance of asthma in chemical warfare victims' (CWV) offspring. The objective of this study was to determine the prevalence of asthma in children of CWV and compare it to asthmatic children in the general population.

**Methods:** Four hundred and nine children from 130 CWV fathers and 440 children from 145 asthmatic parents from two cities in Iran participated in this study. The prevalence of asthma was determined by standard questionnaire released for epidemiological survey of asthma in children and compared between two groups.

**Findings:** The prevalence of asthma in the CWV group was 15%; this was not significantly different from the control group (12.5%). The children of the CWV group reported a significantly greater incidence of wheezing (1.2±3.1 attacks) per year, but the control group reported more severe attacks leading to speech difficulties (3%) and coughing (7%). Regression analysis showed that with increasing family size in the control group, the number of subjects suffering from asthmatic symptoms decreases significantly ( $r=0.86$ ,  $P=0.001$ ).

**Conclusion:** Chemical agents may increase the prevalence of asthma in the offspring of CWV.

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**Key Words:** Chemical Warfare; Sulfur Mustard Gas; Asthma; Family Size

### Introduction

Twenty five years passed from the last exposure of veterans to chemical agents during Iran-Iraq war. Chemical warfare agent such as sulfur mustard causes late complications in organs such as lung, peripheral nerves, skin, and eyes [1-3]. In the early

phase, the most frequent pulmonary complications of chemical warfare agent were Chronic obstructive pulmonary disease (including emphysema), interstitial lung fibrosis and bronchiectasis [4-6]. Some years after the war, the predominant pulmonary complication was

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bronchiolitis obliterans [7,8]. Predominant inflammatory cells in bronchoalveolar lavage were neutrophils and CD8 T lymphocytes [8,9].

Recently chemical warfare victims (CWV) mostly complained of cough, dyspnea and wheezing that are very similar to asthma. These subjects were healthy for a period of time after exposure. Their disease shows some difference from asthma such as a steady state course, resistance to treatment and severity. Our past study showed that 75% of CWV suffered from air way hyper responsiveness [10]. For the time being, these disorders usually are treated with high dose inhaled corticosteroids and long acting beta 2 agonists [11]. An experimental study also showed increased tracheal response to methacholine eosinophilic infiltration due to sulfur mustard in guinea pigs [12]. According to the current evidence that sulfur mustard gas can induce injury to DNA [13], the question raised was, is late pulmonary complications of chemical warfare (such as asthma) generated from a genetic mutation? If so, this genetic predisposition can be passed to offsprings and increase the frequency of lung disease in children like incidence of asthma.

Objective of this study was to determine the prevalence of asthma in the progeny of CWV and compare it to children of asthmatic subjects in general population.

## **Subjects and Methods**

### **Subjects:**

Four hundred nine children from 130 CWV fathers and 440 children from 145 asthmatic parents from two cities of Iran entered this study by simple clinical sampling method.

Parents of case group children complained from dyspnea, cough, wheezing and sometimes hemoptysis. All of them had proven history of exposure to chemical weapons such as nerve or blister agents and experienced skin symptoms after exposure for a period of time. Spirometry revealed obstructive pattern with variable response to bronchodilator. High resolution computed tomography showed air trapping with or without nodular pattern. They were usually

treated with inhaled corticosteroids (Beclomethason dipropionate or Fluticason dipropionate) and inhalation of long acting Beta 2 agonists.

Parents of control group were asthmatic patients proved by 1) history of cough, dyspnea, wheezing and air way hyper responsiveness, 2) increasing of the symptoms during night and in particular seasons, 3) spirometry that showed obstructive pattern with more than 12% increase with bronchodilator or PC20 (Concentration of methacholine needs 20% decrease in FEV1) less than 8mg/l.

The experiments were approved by the Ethical Committee of Mashhad University of Medical Sciences and each subject gave his/her informed consent.

### **Technique and protocol:**

Diagnosis of asthma in children was made by standard questionnaire of European Respiratory Society, released for epidemiological survey of asthma in children (Appendix 1)[14]. The questions were asked from parents. Some questions were added to questionnaire about history of asthma in family of CWV, severity of disease and birthday of children (to know whether they were born before or after the exposure). Severity of obstructive lung disease was classified according to American Thoracic Society recommendations to mild, moderate and severe disease [15].

### **Statistical analysis:**

Sample size was calculated according to 5% alpha error, 80% power and 1/1 ratio of control to case group (400 CWV and 450 control subjects). Mean values for age and spirometric data were quoted as arithmetic mean and standard deviation. In comparing values of spirometric data and frequency of asthma in children between normal and chemical war victims unpaired t-test was used. Analysis of variance was used to test differences between the CWV severity groups. Binary logistic regression analysis was used for evaluation of the effect of cigarette smoking risk, gender, family history of asthma and allergic disease on children's asthma outcome. The relation between family size and frequency of asthma in children was evaluated by regression coefficient. Significance was accepted at  $P < 0.05$ .



**Table 1:** Comparison of demographic data between parents and children of chemical warfare victims and control asthma group

Parameters	Chemical warfare victims	Asthmatic control	Statistics	P-value
Male parent (%)	100	32	$\chi^2=420$	0.0001
Female to male ratio of children	1.00	1.02	$\chi^2=0.02$	0.9
Age of parents [mean (SD) years]	43 (7)	47 ± 11	t=6.11	0.001
Age of children [mean (SD) years]	13.0 (6.6)	19±11.3	t=5.9	0.001
Percent of smoker parents	27%	5%	$\chi^2=64$	<0.001
Parents' positive family history	2.3%	20%	$\chi^2=54$	<0.001

SD: Standard Deviation

## Findings

### General data:

Female to male ratio in CWV children was 1 to 1 and for control asthmatic group was 1.02 to 1 that was statistically different ( $\chi^2=0.02$ ,  $P=0.9$ ). Most important demographic data in children and parents of CWV and control asthmatic group are shown in Table 1. Average age in parents and children of control asthmatic group was significantly higher than in CWV group.

Positive family history of pulmonary disease was noted in control asthmatic group but smoking was more prevalent in CWV group.

### Severity of disease:

Table 2 shows comparison of severity of disease in parents according to clinical staging of asthma. Control asthmatic group was significantly placed in a higher stage of the disease ( $\chi^2=40$ ,  $P=0.0001$ , likelihood ratio=41.5).

### Results in children:

Descriptive data of clinical symptoms in CWV children and control group are shown in Table 3. Comparison of frequency of wheezing was not significantly different between the two groups but the CWV group reported wheezing more than one

episode per year and 3% of CWV group reported severe attacks that caused problem during speech (Odds ratio=5.18,  $^{95\%}$ CI=1.5-17.5), both of which were significantly more than in asthmatic group (Table 3).

On the contrary, cough was reported in 7% of subjects that was not significantly more in CWV group (4%). Night symptoms and symptoms after exercise were not significantly different in the two groups. Totally 15% of CWV group and 12.5% of asthmatic group were asthmatic according to questionnaire that was not statistically different. Risk assessment of underlying risk factors' effect on childrens logistic regression analysis showed that smoking in family history of asthma was not a risk for inducing asthma in CWV children but family history of asthma was a risk for existence of asthma in control group (Table 4).

### Family size:

Fig. 1 shows the frequency of asthmatic involvement in children according to family size. Asthmatic involvement in CWV families with 2 to 4 children was higher than in average of the same family size and in asthmatic families with 1 to 3 children was higher than in average of their group. In families with higher number of children asthmatic involvement decreased significantly.

**Table 2:** Comparison of severity of asthma according to Global Initiative for asthma (GINA) classification in the chemical warfare victims and control asthma group

Group	Asthma stage				Total
	1	2	3	4	
CWV	11 (2.9%)	206 (54.6%)	125 (33.2%)	35 (9.3%)	377
Asthma	5 (1.2%)	171 (39.7%)	149 (34.6%)	106 (24.6%)	431

CWV: Chemical Warfare Victims

**Table 3:** Comparison of results of asthma questionnaire data between children of chemical warfare victims and asthmatics

	CWV	Asthmatic	Statistics	P-value
<b>Wheezing</b>	14% (61/409)	12% (51/440)	$\chi^2= 2.05$	NS
<b>Frequency of wheeze per year [mean (SD)]</b>	1.18±3.1	0.37±1.3	t=4.9	0.0001
<b>Night respiratory symptoms</b>	10% (42/409)	10% (47/440)	$\chi^2= 0.04$	NS
<b>Speech problem caused by attacks</b>	0.7%(3/407)	3% (17/438)	$\chi^2= 9.05$	0.003
<b>Previous diagnosis of asthma</b>	6%(28/409)	7% (35/440)	$\chi^2= 0.37$	NS
<b>Symptoms after exercise</b>	9%(38/408)	6% (30/440)	$\chi^2= 1.78$	NS
<b>Cough</b>	4%(17/409)	7% (32/440)	$\chi^2= 3.78$	0.05
<b>Total of asthmatic children</b>	15% (62/409)	12.5% (55/440)	$\chi^2= 1.21$	NS

SD: Standard Deviation / CWV: Chemical Warfare Victims

Regression analysis showed that with increasing family size in asthmatic group, the subjects that suffered from asthmatic symptoms decreased significantly ( $r=0.86$ ,  $P=0.001$ ). This result was repeated in CWV group with a borderline result ( $r=0.61$ ,  $P=0.059$ ).

## Discussion

This is an epidemiological study to determine the prevalence of asthma in children of chemical warfare victims. Results of this study showed that prevalence of asthma in children of CWV is 15% which is not significantly different from that of children of asthmatic subjects.

Many studies evaluated the prevalence of asthma in Iran by ISAAC questionnaire. A systematic review of these studies showed that prevalence of asthma symptoms in Iranian children is 13.14% (range 2.7%-35.4%) [16,17]. In

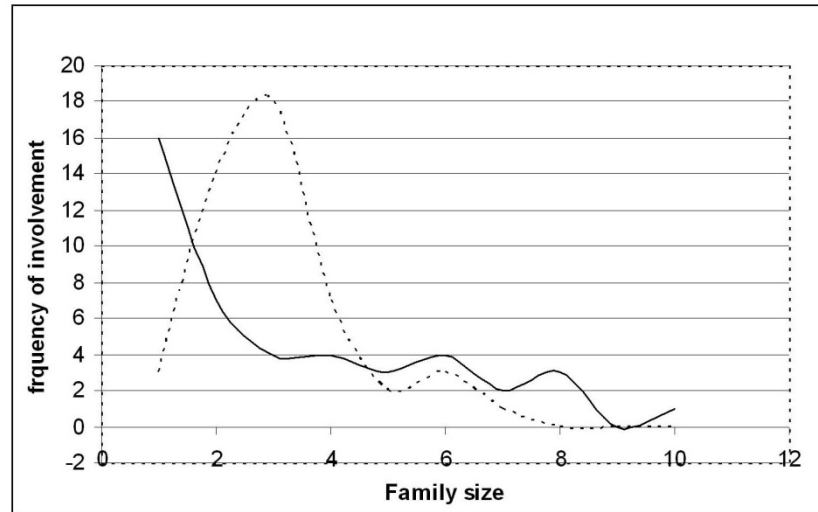
our local region, Boskabady and Karimian estimated the prevalence of asthma in a similar age range of general population [18]. They found that prevalence of asthma was 4.19% in the population studied. So the prevalence of asthma in children of CWV is much higher than that in general population.

According to questionnaire, there was some difference between children of CWV and asthmatics. Children of CWV reported more attacks of wheezing per year but children of asthma group reported more attacks that were more severe. Exposure to cigarette smoke in children of CWV was more frequent than in children of asthma group, while cigarette smoking in the CWV group is similar to that in general population in our region. CWV are a heterogeneous group that suffered from long lasting obstructive lung disease such as bronchiolitis obliterans, asthma, bronchiectasis and chronic bronchitis [2,7]. But they shared in common one factor: exposure to chemical warfare. From multiple agents used in chemical warfare,

**Table 4:** Logistic regression analysis for risk assessment of some underlying constitutional risk factors on coming into existence of asthma in children of chemical warfare victims and control asthma group

Risk factors	Descriptive study		Odd ratio		95% CI		P-value	
	CWV	Asthmatic	CWV	Asthmatic	CWV	Asthmatic	CWV	Asthmatic
<b>Passive cigarette smoking</b>	27%	5%	1.09	1.38	0.28-4.15	0.87-2.2	0.9	0.2
<b>Family history</b>	2.3%	20%	1.99	2.96	0.19-11.54	1.4-6.1	0.1	0.001
<b>Sex (Female/Male)</b>	1/1	1.02/1	1.04	1.34	0.53-2.07	0.72-2.34	1	0.3

CWV: Chemical Warfare Victims / CI: Confidence interval



**Fig. 1:** Relationship between family size and frequency of asthma involvement in children of Chemical warfare victims (dotted line) and control asthmatics (line)

sulfur mustard proved to interfere in host genetic<sup>[13]</sup>. The present study showed that family history of asthma in CWV was significantly lower than in asthma group. It means that chemical warfare not only induced lung disease mimicking asthma but also the victims could inherit it to their offspring and increase prevalence of asthma in the community.

One controversy exists with this conclusion. CWV that entered this study were selected according to proven history of exposure to chemical warfare and presenting pulmonary and dermatologic complications of the agents. By chance these subjects may come from asthmatic families that exist regularly in any society. In reply to this controversy we should consider that before exposure to chemical warfare, history of lung disease in CWV was significantly lower than in asthmatic group and logistic regression analysis showed that family history of lung disease was not a risk factor for asthma in children of CWV. Therefore they did not have the genetic predisposition of asthmatic group. In future some more accurate biologic markers for diagnosis can aid to better selection of subjects suffering from complications of chemical warfare. Fortunately cigarette smoking was not a risk factor for developing asthma in children of CWV and asthmatics. According to proved risk for developing asthma by cigarette smoking, we

believe that parents of our subjects avoided exposing their children to cigarette smoke.

Family size is a protective factor for genesis of asthma<sup>[19]</sup>, which was true also in children of CWV. Its mechanism may relate to protective effect of T<sub>1</sub> helper system on asthma and it seems that asthma in children of CWV is not different from that in other asthmatic subjects.

## Conclusion

Prevalence of asthma in children of CWV is as high as in children from population previously diagnosed as asthmatic. Therefore chemical weapons may spread the asthma in offspring of CWV and their community.

## Acknowledgment

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committee of Islamic Azad University, Mashhad Branch.

**Conflict of Interest:** None

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## Appendix 1

### Questionnaire

Chemical warfare victim [ ]      asthma [ ]

#### Parents:

1-1. Name:

1-2. Gender: Female [ ]    Male [ ]

1-3. Age:...

1-4. Did CWV suffer from lung disease before exposure? Yes [ ]    No [ ]

1-5. Is there any history of lung disease in family of CWV? Yes [ ]    No [ ]

1-6. Smoking history Yes [ ]    No [ ]

1-7. Staging of lung disease

1-8. Mild intermittent [ ]    Mild persistent [ ]    Moderate persistent [ ]    Sever persistent [ ]

#### First Children:

2-1. Age

2-2. Boy [ ]    Girl [ ]

2-3. Born after exposure Yes [ ]    No [ ]

2-4. Has the child ever had wheezing in the chest at any time in the past? Yes [ ]    No [ ]  
If you answered No please skip to question 2-9

2-5. Has the child had wheezing in the chest in the last 12 months? Yes [ ]    No [ ]  
If you answered No please skip to question 2-9

2-6. How many attacks of wheezing has the child had in the last 12 months?  
None [ ]    1 to 3 [ ]    4 to 12 [ ]    More than 12 [ ]

2-7. In the last 12 months, how often, on average, has the sleep of your child been disturbed due to wheezing? Never woken with wheezing [ ]    Less than one night per week [ ]    One or more nights per week [ ]

2-8. In the last 12 months has wheezing ever been sever enough to limit the child speech to one or two words at a time between breaths? Yes [ ]    No [ ]

2-9. Was diagnosis of asthma made in your child? Yes [ ]    No [ ]

2-10. In the last 12 months, has the chest of your child been wheezy during or after exercise?  
Yes [ ]    No [ ]

2-11. In the last 12 months, has the child had a dry cough at night, apart from cough due to cold?  
Yes [ ]    No [ ]

**(Section of child is repeated for other children)**