

Urogenital History in Veterans Exposed to High-Dose Sulfur Mustard

A Preliminary Study of Self-Reported Data

Mohammad Reza Soroush,¹ Mostafa Ghanei,¹ Shervin Assari,¹
Hamid Reza Khoddami Vishteh^{2,3}

Introduction: To date, little information exists regarding urogenital diseases in those who have been exposed to sulfur mustard (SM). We report the self-reported history of urologic conditions and findings on physical examination in a group of male veterans 19 to 26 years after exposed to high-dose sulfur mustard.

Materials and Methods: Data on urologic health conditions of a nationwide health survey were used in this study. This survey included all 289 Iranian male veterans who had been exposed to high doses of SM between 1983 and 1989. Demographic data, exposure-related data, health status, and also self-reported lifetime history of urologic conditions were analyzed. History of benign prostatic hyperplasia, recurrent urinary tract infections, pyelonephritis, urinary calculi, kidney failure, and urogenital neoplasms were specifically concerned.

Results: The mean age of the veterans was 45.0 ± 7.5 years (range, 30 to 75 years). An interval of 19 to 26 years had passed from exposure to SM. Fifty veterans (17.3%) had a positive history of urinary calculi, 25 (8.7%) had recurrent urinary tract infections, 5 (1.7%) had BPH, and 2 (0.7%) had kidney failure. None of them had experienced urogenital malignancies. Neither recurrent urinary tract infections nor urinary calculi were significantly associated with age, medications and their doses, or SM-induced late complications in other organs.

Conclusion: This study adds the prevalence of self-reported urologic conditions to our limited knowledge on SM-exposed veterans' health condition, without finding any link neither to demographic, nor to the severity of health complications related to the SM exposure.

Keywords: chemical warfare, mustard gas, veterans, Urologic diseases, health care surveys

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¹Janbazan Medical and Engineering
Research Center, Tehran, Iran

²Department of Psychiatry,
Medicine and Health Promotion
Institute, Tehran, Iran

³Scientific Writing Network,
Tehran, Iran

Corresponding Author:
Shervin Assari, MD
Psychiatry Department, Medicine
and Health Promotion Institute,
Tehran, Iran
Tel: +98 21 8126 4150
Fax: +98 21 8803 7561
E-mail: cru_common@yahoo.com

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INTRODUCTION

Although sulfur mustard (SM) enters all organs through systemic distribution when used as warfare, until now, the only systems which have been proven to be affected are the lung, skin, and blood.⁽¹⁻⁴⁾ It has not been well-investigated whether SM affects other body organs such as the

urinary tract or neurological and gastrointestinal systems in the long run. The lack of knowledge has precluded ruling out any impairment of these organs by SM to date.⁽⁵⁾ In particular, most previous studies assessing late complications of SM-exposed veterans have neglected the urogenital system.^(6,7)

There is a great body of evidence regarding acute effects of SM on the urogenital system in animal model. Bournsnel and colleagues⁽⁸⁾ showed that radioactive SM diffused rapidly throughout the body after intravenous injection in experiments on rabbits. Activity was retained chiefly in the kidneys, and with approximately 20% of the SM activity being excreted in 12 hours. In rodents, the majority of the injected SM was excreted in the urine within 72 hours.^(9,10) Also, it was shown that several metabolites of SM which may theoretically affect the urogenital system were found in urine.⁽¹¹⁾

Nearly, all we know about the effect of SM on the urogenital system has been derived from studies of acute phase of exposure in animal models,⁽¹²⁻¹⁴⁾ while information on human data, especially on the late phase after exposure, is limited.⁽¹⁵⁾ Given the chemical attacks by Iraq in 1980s, today in Iran, a large population of SM-exposed veterans live with long-term complications. Herein, we report the findings of a survey focusing on the history of urogenital conditions in male veterans exposed to SM, 19 to 26 years earlier.

MATERIALS AND METHODS

Setting

Data presented here is a part of the Veterans Health Survey done by the Janbazan Medical and Engineering Research Center, in Isfahan, Iran, in 2007. In this survey, all veterans exposed to high doses of SM between 1983 and 1989 were selected from all provinces of Iran by census sampling. A total of 345 affected veterans were approached, of whom 289 agreed to participate in the health survey. High-dose exposure was defined as an exposure that has caused acute life-threatening effects which needed aggressive inpatient care during the early stages, accompanied by different chronic complications during the late phase.⁽⁷⁾

Veterans Health Survey

For the Veterans Health Survey, all veterans were invited to a health symposium of veterans held in Isfahan, in 2007. In the first step, baseline information including age, sex, living place (urban/rural), and exposure-related data were

registered. In the second step, the veterans underwent health survey which included a comprehensive review of systems done by 3 internists. In the third step, a through investigation by means of history taking, collection of laboratory data, and physical examination of the organs which have been proved to be affected by SM was done.

Chronic SM-induced complications in the skin, lung, and eye; decompensation rate; and medications and their dosages were recorded. Decompensation rate was defined as the percentage of disability which is determined by a specialized commission in veteran's affair in Iran. The higher the decompensation rate, the poorer the health status of the veterans. This rate determines life time free healthcare and other facilities for the veteran.

Extracted Data

We considered the second part of the Veterans Health Survey, namely comprehensive review of systems which were done by 3 internists who were blinded to data of other parts. We also analyzed the self-reported urogenital conditions including benign prostatic hyperplasia (BPH), recurrent urinary tract infections (UTIs), urinary calculi, and kidney failure. Recurrent UTI was defined as 2 or more infections within 1 year, separated by a negative urine culture, or urosepsis.⁽¹⁶⁾

Statistical Analyses

Data were analyzed with the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Illinois, USA). We reported the frequency of each diagnosed urologic condition and applied the chi-square test and independent sample *t* test or Mann-Whitney test to compare participants with and without recurrent UTIs and urinary calculi. *P* values less than .05 were considered significant.

RESULTS

All of the participants were men. Their mean age was 45.0 ± 7.5 years (range, 30 to 75 years). An interval of 19 to 26 years had passed from exposure to SM to the time of survey (median, 21 years; interquartile range, 2 years). The mean

decompensation rate was $49.0 \pm 15.0\%$ (range, 30% to 70%). Most participants were living in urban areas and were diagnosed with bronchiolitis obliterans. Baseline data are presented in the Table.

Of a total of 289 SM-exposed veterans, 50 (17.3%) had a positive history of urinary calculi. Recurrent UTIs and pyelonephritis were reported by 25 (8.7%) and 2 (0.7%) veterans, respectively. Of the participants, 5 (1.7%) had BPH and 2

(0.7%) suffered from kidney failure. None of the veterans had experienced urogenital malignancies, and no other urogenital diseases were mentioned. Neither recurrent UTIs nor urinary calculi were not significantly associated with age, decompensation rate, interval from exposure to the study time, number of exposures, using preventive equipment at the time of exposure, type of lung disease due to exposure, severity of late respiratory effects due to chemical injury (symptoms severity and spirometry findings), and type or dose of medications.

Baseline Data of Veterans Exposed to Sulfur Mustard

Parameter	Value (%)
Number of patients	289 (100)
Citizens of rural areas	30 (10.4)
Exposure-related data	
Exposed in civil area	22 (7.6)
Exposure times	
1 time	201 (69.6)
> 1 time	88 (30.4)
Using protective equipments	130 (44.9)
Exposure-induced health status	
Dyspnea	
All days	221 (76.5)
Most days	52 (18.0)
Some days	10 (3.4)
Rare	6 (2.1)
No	0
Sputum	
All days	205 (70.9)
Most days	53 (18.3)
Some days	21 (7.2)
Rare	7 (2.4)
No	3 (1.0)
Dyspnea	
All days	250 (86.0)
Most days	32 (11.1)
Some days	6 (2.0)
Rare	0
No	1 (0.3)
Wheeze	
All days	244 (84.4)
Most days	29 (10.0)
Some days	14 (4.8)
Rare	2 (0.7)
No	0
Medications	
Oral corticosteroids	132 (45.7)
Inhaled Corticosteroids	210 (72.2)
Diagnosis of lung disease	
Bronchiolitis Obliterans	101 (34.9)
Chronic Bronchitis	91 (31.5)
Bronchiectasis	28 (9.7)
Asthma	37 (12.8)

DISCUSSION

According to our findings, 19 to 26 years after exposure to high-dose SM, 17.3%, 8.7%, 1.7%, 0.7%, and 0.7% of the veterans reported a history of urinary calculi, recurrent UTIs, BPH, pyelonephritis, kidney failure, respectively. Of interest, there were no reports of urogenital malignancies in this cohort of veterans. In addition, the history of these urologic conditions had no association with age, medications, and late complications in other organs due to SM exposure.

Self-reported data collected in surveys, although lack strong evidence, provide the primary information for a field, when we have less knowledge in a field. In the case of SM-related health problems, documented evidence on urological diseases is limited. In the United States, veterans exposed to SM reported a frequency of 3% for bladder diseases, 4% for chronic kidney disease, 4% for prostate disease, and 0.5% for kidney neoplasms.⁽¹⁷⁻¹⁹⁾ In these reports, all exposed veterans had participated in chamber tests, with full equipment, which means all had been exposed to low-dose SM. Information on the long-term effects of high doses of SM is lacking, and we have to rely on self-reported information. In our study, all of the participants had been exposed to high levels of the toxic gas, several of them without any preventive equipment. They were not only symptomatic, but also admitted to a hospital in the early phase.⁽¹⁷⁾

In the acute phase of exposure to SM, early extraction of the toxin from urine has been reported.^(19,20) Also, the extraction of high levels

of SM from the kidney was documented 7 days after death of an Iranian soldier due to high-dose exposure.⁽²¹⁾ Animal models have shown that following a single exposure to SM, the level of gas is highest in the kidneys, even higher than that in the lungs and other organs; therefore, this can be hypothesized that SM exposure may have some subsequent biological effects on the urogenital system.⁽⁸⁾ However, the most prevalent late complication after exposure is seen in the respiratory system. In order to investigate the possible link between the reported urologic conditions and severity of exposure, we assessed their possible link with severity of respiratory complications measured by severity of symptoms and also spirometry indexes. Such measures have been used previously as an indicator for severity of exposure.⁽²²⁾ We did not find any association of urologic conditions with this index of severity of SM exposure.

We did not have a control group from among the general population, and thus, we cannot draw a definite conclusion whether the frequency of the assessed urological conditions were higher than those of the general population in Iran or not. In addition, different definitions for the urologic outcomes make it difficult to compare our self-reported information with the published literature. Concerning recurrent UTIs, we assume that SM-exposed patients in our study had a relatively high rate of the disease. We do not have distinctive nation-based information on the prevalence of UTI in men, but it is speculated that UTI prevalence in male population is low. On the other hand, the incidence of UTI rises dramatically after the age of 50 years.⁽²³⁻²⁵⁾ Therefore, age-dependent nature of the disease precludes conclusion. In the United States, bacteriuria is seen in 0.1% of young men, and this rate reaches 10% in men older than 65 years old.⁽²⁴⁾ Whereas, symptomatic recurrent UTIs was reported in 8.7% of our patients whose age ranged between 30 and 75 years. Most of these patients had been receiving medications for several years, such as systemic corticosteroids, and they had experienced several hospitalizations and interventions. Thus, regardless of the effect of SM, suffering from recurrent UTIs is anticipated in such patients.

A positive history of urinary calculi was reported by 17.3% of the patients in our study, which seems to be high. It has been shown that the lifetime prevalence of urinary calculi is 10% in the United States, and 1 of 8 men experience it before the age of 70 years.⁽²⁶⁾ The frequency of BPH, however, seems to be in line with our national data; in Iran, BPH was reported in 1.2% of men aged between 40 and 49 years and in 36% of those older than 70 years.⁽²⁷⁾ Furthermore, kidney failure was seen in only 2 of 289 patients who participated in our study. Nafar and colleagues⁽²⁸⁾ showed that in 2007, the prevalence of end-stage renal disease was estimated to be 0.04%.

This cross sectional study describes the frequency of diagnosed urologic conditions in the SM-exposed population of Iranian former veterans. As a result, we cannot rule out or confirm the possible links between SM exposure and urogenital health. Further research is needed using control groups of nonexposed Iranian men. We recommend series of research projects to be conducted by nephrologists, urologists, and toxicologists in these populations to assess any possible link between chronic urologic conditions and high-dose SM exposure. In such studies, the other risk factors of urologic conditions should be assessed, as well,⁽²⁹⁾ such as vesicoureteral reflux and bladder disorders. Lack of data on the patients' condition before the exposure was a limitation of our study. Collecting such data is difficult in these veterans who were involved with chemical attacks more than 15 years ago. Overall, the frequencies of UTIs and urinary calculi in their self-reported history seem to be higher than their prevalence in the general population; however, we cannot make a definite conclusion about the effect of SM on these conditions. Also we should mention that as we did not use any malignancy screening, we cannot be sure about the absence of urogenital neoplasms in the studied sample. This is still a controversy if SM is carcinogen or not⁽³⁰⁾; however, there are reports of such effects, most of which are extracted from animal data, and human data is sparse.^(2,30)

CONCLUSION

To all we now about chronic urogenital effects of

SM exposure in human—which is very few—this study adds the prevalence of self-reported urologic conditions, without finding any link neither to demographic, nor to the severity of health complications related to the SM exposure.

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CONFLICT OF INTEREST

None declared.

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EDITORIAL COMMENT

In 1985, the autopsy of body tissue and fluids of an Iranian man who had died 7 days after exposure to sulfur mustard (SM) showed that concentration of SM in the kidney is several times higher than that in the liver, spleen, lung, muscle, and blood.⁽¹⁾ It is interesting for me as a pharmacologist that late effects of SM after a high-dose single exposure to SM is possible. By other means, SM may affect most of the organs, because it enters most systemic distribution when used as warfare. The urogenital system is not an exception. Unfortunately, most of the research on late effects of SM have focused on negative impact of this toxic gas on the lung, skin, eyes, and blood.⁽²⁻⁷⁾ Do urologists and nephrologists know how they should approach to the late health effects of SM-exposed veterans? Unfortunately, Iran is within the few countries with massive single high-dose exposures, and clinicians cannot easily search the literature for such information. The literature should be made in Iran, and it seems a must for Iranian scientists to investigate all other possible effects of SM.

As the literature shows, very few information exist regarding the urogenital system in those who have been exposed to SM, and in this regard, the current study by Soroush and colleagues has provided us the information on medical history of urological conditions. Self-reported data of medical history is considered as a step forward,⁽⁸⁾ but much is remained in this regard. Further studies may need control groups and comprehensive urological evaluations such as imaging and more specific investigations. In this secondary analysis of a health survey conducted by the Janbazan Medical and Engineering Research Center, beside sociodemographic and exposure-related data, history of urologic conditions, namely benign prostatic hyperplasia, recurrent urinary tract infections, pyelonephritis, urinary calculi, kidney failure, and urogenital

neoplasms have been reported. The most reported conditions included urinary calculi (17.3%) and recurrent UTIs (8.7%). The interesting point for me is the no report of urogenital neoplasms. Sulfur mustard is considered as a “suspected carcinogen,⁽⁹⁾” and carcinogenicity of a single high-dose exposure has not been supported by the available scientific evidence. It is the long-term occupational exposures which have named SM as a carcinogen,⁽¹⁰⁾ and this is not related to what we face in our veterans in Iran.

Yunes Panahi

*Research Center of Chemical Injuries and Nephrology Urology Research Center, Baqiyatallah Medical Sciences University, Tehran, Iran
E-mail: yunespanahi@yahoo.com*

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