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Evaluation of relationship between the serum levels of inflammatory mediators and ocular injuries induced by sulfur mustard: Sardasht-Iran Cohort Study

Hassan Ghasemi [a,b], Tooba Ghazanfari [b,c,*], Roya Yaraee [b,c], Mohammad Ghassemi-Broumand [d], Mohammad R. Soroush [e], Shahryar Pourfarzam [f], Zahra Masdari [b], Soghrat Faghihzadeh [g], Mahmoud Babaei [h], Mohammad A. Javadi [d], Yoshiaki Kiuchi [i], Mohammad M. Naghizadeh [b,j], Parviz Owlia [l], Zuhair M. Hassan [k]

[a] Department of Ophthalmology, Shahed University, Tehran, Iran
[b] Immunoregulation Research Center, Shahed University, Tehran, Iran
[c] Department of Immunology, Shahed University, Tehran, Iran
[d] Department of Ophthalmology, Shahid Beheshti University (M.C), Tehran, Iran
[e] Janbazan Medical and Engineering Research Center (JMERC), Tehran, Iran
[f] Department of Internal Medicine, Shahed University, Tehran, Iran
[g] Department of Biostatistics, Tarbiat Modarres University, Tehran, Iran
[h] Baqiyatallah University of Medical Sciences, Tehran, Iran
[i] Department of Ophthalmology Hiroshima University, Hiroshima, Japan
[j] Fasa University of Medical Science, Fasa, Fars Province, Iran
[l] Department of Microbiology, Shahed University, Tehran, Iran
[k] Department of Immunology, Tarbiat Modares University, Tehran, Iran

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ABSTRACT

Ocular damages induced by sulfur mustard (SM) are the important problems in exposed patients. The damaging mechanisms are not clearly understood. In the present study the relationship between the serum levels of inflammatory mediators and ocular injuries induced by SM was evaluated.
Bulbar conjunctiva and limbal tissue abnormalities were significantly more frequent in the expose versus control group ($P=0.004$ and 0.048 respectively). The serum levels of IL-1α and TNF-α in the exposed group with and without Slit lamp findings were significantly lower than their counterpart in the control group. The serum levels of IL-1β in the exposed group with Slit lamp findings were significantly lower than their counterpart in the control group. The serum levels of IL-1β in the controls with Slit lamp findings were significantly higher than the controls without Slit lamp findings. The serum levels of IL-1Ra and MMP-9 in the exposed group with and without Slit lamp findings do not display any significant differences as compared to the similar controls. The serum levels of IL-6 in the exposed group with or without Slit lamp findings were significantly lower than their counterpart in the control group ($P=0.048$ and 0.008 respectively). The serum titers of the CRP and RF in the exposed group without Slit lamp findings were significantly elevated versus their counterpart in the control group ($P=0.004$ and 0.011 respectively). The serum levels of these inflammatory cytokines except for IL-1Ra and MMP-9, decreased in SM exposed subject independent of ocular problems. More local studies on the eyes are needed to clarify the exact role of this cytokines in ocular problems of chemical.

1. Introduction

Cytokines are best known as mediators of host defense responses to infection and other environmental stresses [1]. Inflammation with subsequent infiltrations of leucocytes and connective tissue cells together with the release of cytokines is essential for healing tissue damages [2]. Matrix Metalloproteinases (MMPs) are a great family of zinc-containing and calcium-dependent endopeptidases which are responsible for tissue remodeling and extracellular matrix (ECM) degradation [3]. CRP and RF are the two important markers in inflammatory disorders for the diagnosis, prognosis and the need for more intensive treatment irrespective of the duration of the disease [4].

Sulfur mustard (SM) is an alkylating agent that induces short and long term toxicity on various tissues. Moist tissues such as the eyes and respiratory tract are particularly affected by SM [5–7]. SM reacts rapidly with the ocular tissues and after a latent period of a few hours

* Corresponding author. Department of Immunology, Medical Faculty, Shahed University, Tehran, Islamic Republic of Iran. P.O. Box: 14155-7435. Tel.: +98 2188964792; fax: +98 2188966310.
E-mail addresses: ghazanfari@shahed.ac.ir, tghazanfari@yahoo.com (T. Ghazanfari).

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Table 1
Comparisons of Slit lamp findings (signs) in SM exposed and control groups.

Slit lamp findings	Study groups		*P* value
	Control	Exposed	
Lids			
Normal	125(97.7%)	359(97.8%)	0.914*
Abnormal	3(2.3%)	8(2.2%)	
Bulbar conjunctiva			
Normal	126(98.4%)	333(90.7%)	0.004*
Abnormal	2(1.6%)	34(9.3%)	
Limbal tissue			
Normal	128(100.0%)	356(97.0%)	0.048**
Abnormal	0(.0%)	11(3.0%)	
Tear status			
Normal	117(91.4%)	316(86.1%)	0.119*
Abnormal	11(8.6%)	51(13.9%)	
Cornea			
Normal	127(99.2%)	358(97.5%)	0.247**
Abnormal	1(.8%)	9(2.5%)	

The ophthalmologic assessment was carried out by a clinician using a Slit lamp biomicroscope. A comparison was undertaken between the control and exposed groups. Data presented as: number (percentage).
**P* value was computed with chi square.
***P* value was computed with Fisher exact test.

severe eye pains, photophobia, excessive tearing and temporary blindness may occur. The injury is mostly restricted to the anterior segment of the eye but may cause long-lasting ocular problems. Although late complications of SM poisoning in the skin, eyes and respiratory system are mainly due to the direct toxic effects; the neuromuscular, hematological and immunological complications are probably the result of systemic toxicity [8]. Late ocular complications may appear as neovascularization, recurrent erosions and recurrent corneal edema (delayed keratitis). In the chronic phase ocular surface changes include: blepharitis, decreased tear meniscus layer, limbal ischemia, conjunctival vascular abnormalities, corneal scar or opacity, neovascularization, thinning, lipid and amyloidal deposits, epithelial defects and irregularity [9]. The pathophysiologic features of these changes are not clearly identified. Excised conjunctival and corneal specimens revealed a mixed inflammatory response without any specific features. Based on the clinical appearance of the lesions and the histopathologic findings, an immune-mediated component seems possible [10]. Penetrating keratoplasty (PK) in chronic or delayed-onset mustard gas keratitis should be considered as a high-risk graft; however, with appropriate management, graft clarity and visual outcomes may be favorable [11]. Although pathogenic mechanisms are unknown, interleukins seem to be involved in the cornea and some other ocular inflammatory disorders [12,13]. The role of MMPs in inflammation and destruction of local tissues in ocular problems which is followed by angiogenesis has been showed by previous studies [14,15]. CRP is an indicator of (local) inflammatory activity and a kind of direct and quantitative measure for the acute phase reaction and provides adequate information of the actual situation [16]. The serum levels of CRP increased in some ocular disorders such as age-related macular degeneration (AMD) or mild cataract [17]. It seems that an inflammatory process may be responsible for the delayed ocular problems in the SM exposed patients [9].

The present study was performed to analyze the concentrations of IL-1α, IL-1β, IL-1Ra, TNF-α, MMP-9, IL-6, CRP and RF in the serum and their relations with ocular problems in the SM exposed participants 20 years after exposure.

2. Materials and methods

2.1. Study design and participant

A comprehensive historical cohort study in Sardasht-Iran 20 years after SM exposure was established as Sardasht-Iran Cohort Study (SICS) [18]. This study was approved by the Ministry of Health of Iran, Shahed University and the Board of Research Ethics of Janbazan Medical and Engineering Research Center. A written informed consent was obtained from all the subjects in the study. The details of SICS were reported previously [18]. There were 372 exposed and 128 control participants.

2.2. Clinical evaluation

A complete ophthalmologic assessment including ocular history, visual acuity changes, ocular examination using a Slit lamp biomicroscope (Nidek model, Gamagori, Japan), for evaluation of the lids, tear meniscus layer, bulbar conjunctiva and limbal tissue, cornea and anterior segment was done. Evaluation of the posterior segment was carried out using direct and indirect ophthalmoscope (Heine K 180 Ophthalmoscope Germany and Heine Omega 100 EN20-1 Binocular Indirect Ophthalmoscope Germany). Final ophthalmologic assessments were recorded using the criteria verified by the Medical Committee of the Foundation of Martyr and Veterans Affairs [19].

2.3. Serum samples collection

Peripheral blood was drawn using Vacutainer tubes (BD Biosciences). The sera were separated by 20 min centrifugation at 2000×g (4 °C), aliquoted and stored at −80 °C until laboratory measurements.

2.4. Cytokine measurement

Human IL-1α, IL-1β, IL-1ra, TNF-α and MMP-9 DuoSet ® ELISA Development kits (R&D Systems) were used to measure the IL-1α, IL-1β, IL-1ra, TNF-α and MMP-9 levels in the sera. Primary antibody was mouse anti-human and biotinylated goat anti-human was the secondary antibody. Standards of the kits were diluted with 1% BSA in PBS. Wash buffer was 0.05% Tween 20 in PBS, and 1% BSA in PBS used as block buffer. Used PBS in wash and block buffer contained 137 mM NaCl, 2.7 mM KCl, 8.1 mM Na_2HPO_4, and 1.5 mM KH_2PO_4. Rheumatoid Factor Screen ELISA kit (DRG Instruments GmbH; Germany) was used to measure Rheumatoid Factor in the sera. CRP quantitative diagnostic kit was used to measure CRP in sera by photometric method. In this method CRP in the sera was made complex with polyclonal antibody against CRP. ELISA reader and washer were Stat-Fax 2100 and Stat-Fax 2600 (USA) respectively.

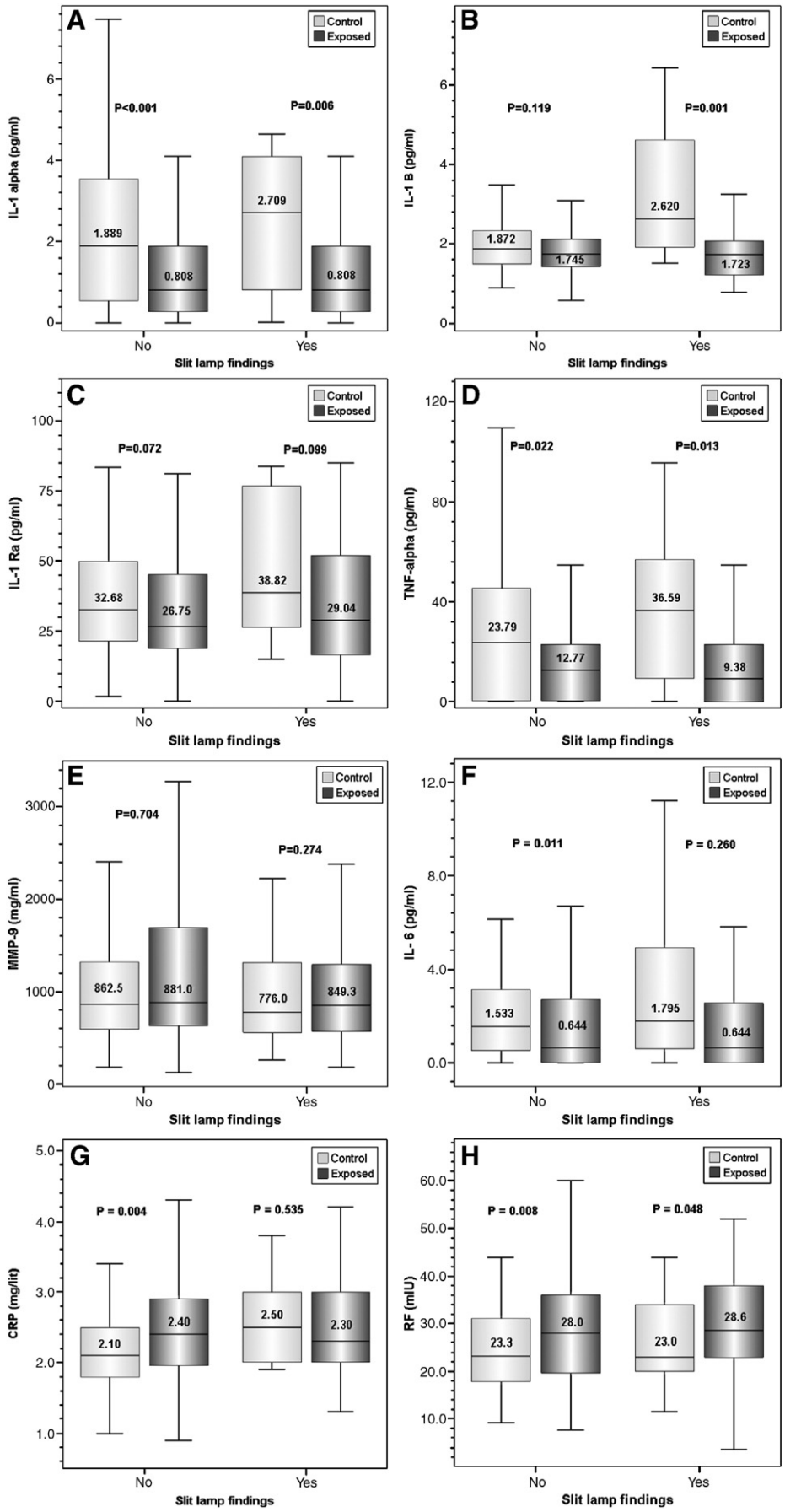
2.5. Statistical analysis

Statistical comparison of Slit lamp finding between the control and exposed groups was done with chi square and Fisher exact test. Comparison of the serum levels of cytokines between groups was performed using the Mann–Whitney test. Differences were considered as statistically significant when $P \leq 0.05$ and are presented as median (first and third quartiles). Data analysis was performed using SPSS software version 13.0 (Chicago, Illinois, USA). Because the rates of sample size regarding ocular problems in the control group were lower than the required size, we pooled all of the Slit lamp abnormalities for each group into one cohort analysis.

3. Results

3.1. Clinical findings

There were no statistically significant differences between the age and marital parameters between the exposed and control groups, demographic information was published previously [18]. Lids, bulbar conjunctiva, limbal tissues, tear and corneal status were evaluated by Slit lamp biomicroscope. Bulbar conjunctiva and limbal tissue abnormalities


A
Control
Exposed
P<0.001
P=0.006
IL-1 alpha (pg/ml)
1.889
0.808
2.709
0.808
No
Yes
Slit lamp findings
B
P=0.119
P=0.001
IL-1 B (pg/ml)
1.872
1.745
2.620
1.723
C
P=0.072
P=0.099
IL-1 Ra (pg/ml)
32.68
26.75
38.82
29.04
D
P=0.022
P=0.013
TNF-alpha (pg/ml)
23.79
12.77
36.59
9.38
E
P=0.704
P=0.274
MMP-9 (mg/ml)
862.5
881.0
776.0
849.3
F
P = 0.011
P = 0.260
IL- 6 (pg/ml)
1.533
0.644
1.795
0.644
G
P = 0.004
P = 0.535
CRP (mg/lit)
2.10
2.40
2.50
2.30
H
P = 0.008
P = 0.048
RF (mIU)
23.3
28.0
23.0
28.6

were significantly more frequent in the exposed group versus control group ($P=0.004$ and 0.048 respectively) (Table 1).

3.2. Serum levels of inflammatory markers in studied groups

The serum levels of inflammatory markers including IL-1α, TNF-α, IL-1β, IL-1Ra, MMP-9, IL-6, CRP and RF in the control group with and without Slit lamp findings were not significantly different (Fig. 1). However, IL-1β in the controls with positive Slit lamp findings were significantly higher than the controls without Slit lamp findings ($P=0.01$) (Fig. 1, B).

The serum levels of all studied inflammatory markers in the exposed group with and without Slit lamp findings did not show significant differences (Fig. 1, A to H).

3.3. Comparison of the serum levels of inflammatory markers between studied groups

Comparisons of the control and exposed groups showed that the serum levels of IL-1α in the exposed group either with or without Slit lamp findings were significantly lower than their counterpart in the control group ($P=0.001$ and 0.006 respectively) (Fig. 1, A). TNF-α in the participants of exposed group with and without Slit lamp findings were also significantly lower than their counterpart in the control group ($P=0.022$ and 0.013 respectively) (Fig. 1, D). The similar decrease was found in the serum levels of IL-1β ($P=0.001$) (Fig. 1, B). However, IL-1Ra and MMP-9 in the participants of the exposed group with and without Slit lamp findings did not display any significant differences with their counterpart in the control group (Fig. 1, C and E). The serum levels of IL-6 in the exposed group with or without Slit lamp findings were significantly lower than their counterpart in the control group ($P=0.048$ and 0.008 respectively) (Fig. 1, F). The serum titers of the CRP and RF in the exposed group without Slit lamp findings were significantly elevated versus their counterpart in the control group ($P=0.004$ and 0.011 respectively) (Fig. 1, G and H).

4. Discussion

Inflammatory cytokines play a major role in both acute and chronic inflammatory conditions including ocular problems [12,13,20]. Studies based on the levels of inflammatory cytokines in SM intoxicated people are very rare. Our findings in SICS showed that inflammatory markers including IL-1α, IL-1β, IL-1Ra and TNF-α were decreased 20 years after SM exposure [21]. In this paper we evaluated the serum levels of IL-1α, TNF-α, IL-1β, IL-1Ra, MMP-9, IL-6, CRP and RF in a SM intoxicated population in relation with ocular problems. As the results show the serum levels of inflammatory cytokines including IL-1α, TNF-α, IL-1β and IL-6 in the exposed participants with ocular surface problems were significantly lower than their counterpart in the control group, and in those exposed participants without ocular surface problems IL-1α, TNF-α and IL-6 were significantly lower than their counterpart in the control group. Conversely, the serum titers of the CRP and RF in the exposed participants without ocular problems were significantly higher than the control participants without ocular problems. IL-1 is one of the essential factors in wound-healing [22]. Chronic down-regulation of IL-1β inhibits the programmed wound-healing process in bulbar conjunctiva and possibly affected on the ocular surface damage. Moreover, it was reported that recovery of blood perfusion from ischemic change is markedly decreased in IL-1β knock-out (−/−) mice and IL-1β plays an important role in VEGF-mediated neovascularization [23].

There were not any significant differences between the serum levels of MMP-9 in the exposed and control groups with or without ocular problems. There has been no other report on the serum levels of IL-1α, TNF-α, IL-1β, IL-1Ra, MMP-9, IL-6, CRP and RF especially in association with their ocular surface problems in mustard gas exposed patients. Many studies have undertaken the evaluation of local immune responses and detection of the cytokine levels in the eye as the target organ of inflammations in other clinical complications [24,25]. However, it seems that parallel systemic immunological responses have been less considered. In some instances local immunological responses are parallel and in relation with systemic immunological responses or vice versa [26,27].

The result of this study also showed that the serum levels of IL-1β in the controls with positive Slit lamp findings were significantly higher than the controls without Slit lamp findings ($P=0.01$), although there are associations between ocular surface problems and the other three markers (IL-1α, IL-1Ra and TNF-α) in the control group but they were not statistically significant. It has also been reported that the pro-inflammatory mediators of IL-1β, IL-8, TNF-α and IL-6 may play an important role in acute SM injuries [28]. However, the results of this study showed that the serum levels of inflammatory cytokines in exposed cases with or without Slit lamp findings are decreased compared to their counterpart in the control group. It is noteworthy that in contrast to the control no difference was found between exposed group with and without Slit lamp findings.

In the case of MMP-9, there is no study to evaluate the serum levels of MMPs in patients with delayed complications of SM. Some in vitro and animal model studies have reported the association of acute SM complications with changes in MMP expression [29–31]. In a study on mice ear skin 7 days after exposure to SM, relative levels of MMP-9 mRNA and protein were increased 27- and 9-folds respectively compared to the control group [31]. A study by Jacqueminet et al. showed an elevation in circulating level of MMP-9 in type 1 diabetic patients with retinopathy [14]. Chronic inflammation in diabetic retinopathy is followed by neovascularization and the production of angiogenic factors [32]. Neovascularization is reported in 70.8% of chronic ocular injuries in the SM exposed subjects and it is reported as one of the causes of corneal destruction which is known as keratopathy induced by SM [10]. In definition, corneal neovascularization is a disease process involving the abnormal growth of new blood vessel into avascular corneal tissue [33,34]. Based on the evidences on the role of MMP-9 in inflammation and neovascularization, it was expected that local and circulating MMP-9 in the SM exposed people with ocular complications are altered, but our data in this study revealed at least the serum level of MMP-9 does not display any association with ocular complications in SM participants. To clarify the role of MMP-9 in pathogenesis of long term ocular complications in SM exposure, it is necessary to assess this inflammatory marker in local samples of eye including tear or ocular tissues. Higher levels of systemic inflammatory markers including CRP and IL-6 are associated with progression of some ocular disease such as age-related macular degeneration (AMD) [35,36], retinal venular diameter changes [37] and even in diabetic retinopathy [38,39]. This is true in the case of the Rheumatoid Factor (RF) in the juvenile chronic arthritis with ocular involvement [40]. In this study the serum levels of IL-6 in the exposed with or without Slit lamp findings were significantly lower than the normal similar controls, on the contrary the serum titers of CRP and RF were significantly higher in the exposed group. Another immunological mechanism may be implicated in this regard.

In conclusion, the results of this study showed that systemic immunological responses in cases of inflammatory markers including IL-1α, IL-1β, IL-1Ra, TNF-α and IL-6 are decreased in the SM exposed

Fig. 1. Serum levels of inflammatory markers in SM exposed and control groups. Participants who had any Slit lamp abnormalities were categorized as "Yes" and those who did not have Slit lamp findings were categorized as "No". A: IL-1α, B: IL-1β, C: IL-1Ra, D: TNF-α E: MMP-9, F: IL-6, G: CRP and H: RF. Data represented as median (first and third quartile). *P* value represents the comparison of serum levels of inflammatory markers between control and exposed groups (Mann–Whitney).

participants, but increased in the case of the CRP and RF, in comparison with the control group, but their direct relations to ocular surface problems yet remain for further investigations. The serum levels of MMP-9 were not significantly different in the SM exposed subjects and controls with or without ocular problems.

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