Original Article

Association between Acne and Serum Pro-inflammatory Cytokines (IL-1α, IL-1β, IL-1Ra, IL-6, IL-8, IL-12 and RANTES) in Mustard Gas-Exposed Patients: Sardasht-Iran Cohort Study

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Abstract

Background: Acne vulgaris is a very common chronic inflammatory disorder, yet its pathogenesis is not clearly understood. As part of the SICS, this study was conducted to evaluate the association between the incidence of acne vulgaris in sulfur mustard-exposed subjects (20 years after the exposure) and serum levels of proinflammatory cytokines (IL-1α, IL-1β, IL-1Ra, IL-6, IL-8, IL-12 and RANTES) in an attempt to better understand the pathogenesis of long-term skin disorders of these individuals.

Methods: Serum concentrations of cytokines (IL-1α, IL-1β, IL-1Ra, IL-6, IL-8, IL-12 and RANTES) were measured using sandwich ELISA technique.

Results: The median of serum levels of IL-1β, IL-8 and RANTES were significantly higher in the exposed patients with acne than those without acne (P = 0.05, 0.03 and 0.001 respectively). There was no significant difference in serum levels of IL-1α, IL-1Ra and IL-6 between the exposed subgroups.

Conclusion: We found a positive association between serum levels of pro-inflammatory cytokines (IL-1β, IL-8, IL-12 and RANTES) and acne among sulfur mustard-exposed population.

Keywords: Acne, cytokines, mustard gas, Sardasht-Iran cohort study

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Introduction

Sulfur mustard (SM) is an alkylating agent with cytotoxic, mutagenic, and vesicating properties.[1] Exposure to SM leads to short- and long-term adverse effects on multiple organs, especially the skin, the eyes, the respiratory tract and the immune system throught not yet fully understood mechanisms.[2] There have been several studies on cutaneous complications of SM exposure in Iranian SM victims. The late skin lesions are pigmentation disorders, dry skin, eczema, cherry angioma, atrophy and uriticaria.[2–4] The incidence of acne was reported to be 6.6% in SM-exposed group of Sardasht 20 years after SM exposure in SICS.[3] However, there are various records in different groups of Iranian SM exposed individuals.[5] A record acne prevalence of 11% was reported by Emadi *et al.* 14 to 20 years after wartime exposure to sulfur mustard gas.[6]

Acne vulgaris is a very common chronic inflammatory disorder of the sebaceous follicles; the pathogenesis of acne appears to be multifactorial and is not clearly understood. *Propionibacterium acnes* (*P. acnes*), an anareobic bacterium, plays an important role in development of these inflammatory lesions.[7] Recent studies have suggested that inflammatory processes play a key role in the development of acne vulgaris. They also indicate that bacterial infection is not necessary for expression of pro-inflammatory cytokines in the pilosebaceous unit. Therefore, acne vulgaris is likely to be a genuine inflammatory disorder and recent evidence supports a model of acne pathogenesis in which the inflammatory events begin early in the pathogenic process and before clinical detection of the acne lesion.[8,9]

Cytokines are soluble mediators, which act as messengers of the immune system. A recent study of biopsy samples from patients with acne vulgaris showed that expression of inflammatory mediators is upregulated, suggesting an alternative link between *P. acnes* and release of inflammatory mediators.[10] *P. acnes* induces production of pro-inflammatory cytokines, including IL-1β, IL-8, IL-12 and tumor necrosis factor-α via a toll-like receptor-2 (TLR2) dependent mechanism.[11,12] Serum IL-6 levels were significantly higher in patients with acne compared with healthy control subjects, suggesting a role for IL-6 in acne-rosacea pathogenesis.[13]

We have previously reported that in SM exposed individuals with skin findings after 20 years, serum levels of pro-inflammatory cytokines (IL-1α, IL-1β, IL-1Ra and TNF-α) were lower compared to healthy volunteer controls.[14] As part of the SICS, this study was conducted to evaluate the association between the incidence of acne vulgaris and serum levels of pro-inflammatory cytokines (IL-1α, IL-1β, IL-1Ra, IL-6, IL-8, IL-12 and RANTES) in SM-exposed subjects 20 years after the exposure in an attempt to understand the skin disorder's pathogenesis.

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Materials and Methods

Study design and participants

Details of the study design and methodology of the SICS have been reported previously.[1] Briefly, 372 male volunteers from Sardasht with a history of SM exposure in June 1987 and 128 unexposed sex/age matched control from the unexposed town of Rabat were recruited. SICS was initiated in 2006 and the clinical evaluations and samples collection were performed in June 2007. The experiments were completed during 6 months. In this study, all SICS participants were included and divided into 4 groups: 1) SM exposed group with acne disorder, 2) SM exposed group without acne disorder, 3) control group with acne and 4) control group without acne disorder. Complete methodological details of the SICS as well as demographic information have been reported previously in the original methodology paper.[1]

We selected a population with complete information on both clinical evaluation and immunological test. Therefore, our sample size diminished to 345 persons in exposed and 124 persons in control groups.

Ethical considerations

The study was approved by the Ethical Committee of Board of Research Ethics of Janbazan Medical and Engineering Research Center (JMERC), the Board of Research of the Ministry of Health and Medical Education, and Shahed University. Volunteers who signed an informed consent were recruited.

Clinical evaluation

A dermatologist physically examined every volunteer; acne was diagnosed based on clinical examination and appearance of the lesion.[3] Then, SM-exposed and control groups were divided into two subgroups based on the presence of acne disorder.

Serum preparation

Blood drawn into non-treated Vacutainer tubes (BD Biosciences) was used for serum preparation. After clotting, sera were isolated, labeled, aliquoted and kept at −80°C until use.

Cytokine measurement

Human IL-1α, IL-1β, IL-1Ra, IL-6, IL-8, IL-12 and RANTES DuoSet® ELISA Development Kits (R&D Systems) were used to measure serum cytokine levels. This assay employs the quantitative sandwich enzyme immunoassay technique. The ELISA reader of Stat-Fax 2100 and the ELISA reader washer of Stat-Fax 2600 (USA) were used.

Statistical analysis

The data are presented as mean (SD) and median (first and third quartiles). Immunological parameters had profound departure from normal distribution. Therefore, nonparametric Mann-Whitney test was used for statistical comparison of cytokines between the study groups. *P*-values less than 0.05 were considered as statistically significant. Analyses of the data were performed using SPSS software version 18.0 (Chicago, IL, USA).

Results

The number of patients with acne disorder was 24 (6.6%) in the SM-exposed group and 6 (4.7%) in the control group of SICS.[3]

Serum levels of IL-8

As shown in Table 1, a significant ($P < 0.05$) difference in the level of IL-8 was seen between the exposed subgroups with acne (n = 23; median: 18.765) and those without acne (n = 321; median: 12.337). Additionally, the median of serum levels of IL-8 in the SM-exposed participants with no acne disorder was significantly ($P = 0.002$) lower than the matched non-exposed control group (14.928 pg/mL). There was no significant difference between the level of IL-8 in individuals with acne and the control group without acne.

Serum levels of RANTES

As shown in Table 2, a significant ($P = 0.001$) difference in the level of RANTES was seen between the exposed subgroups with acne (n = 23; median: 1231) and those without acne (n = 322; median: 842.65). In addition, the median of serum levels of RANTES in the SM-exposed participants without acne disorder (1.72 pg/mL) was significantly ($P < 0.000$) lower than the matched non-exposed control group (1313 pg/mL) while there was no significant difference between the individuals with acne and the control group without acne.

Serum levels of IL-1β

As shown in Table 3, a significant ($P < 0.05$) difference in the level of IL-1β was seen between the exposed subgroups with acne (n = 23; median: 1.935) and without acne (n = 320; median: 1.72).

Moreover, the median of serum levels of IL-1β in the SM-exposed

Table 1. Association of serum levels of IL-8 in SM-exposed and control groups with acne.

Study groups	(Diagnosis) Acne	IL-8 (CXCL8) (Serum)						P-value[1]	P-value[2]	P-value[3]
		N	Median	Q1	Q3	Mean	SD			
Control	No	119	14.928	10.656	23.403	24.564	27.235			
	Yes	4	16.158	12.343	37.428	24.885	21.144			
Exposed	No	321	12.337	7.612	20.769	18.890	21.998	**0.002**		**0.030**
	Yes	23	18.765	10.010	36.161	28.987	30.590		0.397	

The serum levels of IL-8 in volunteers who had (Yes) and who did not have acne (No) were assessed and a comparison was undertaken between the control and exposed groups, as well as, within each groups.
***P*-value[1]:** comparison between exposed participants who did not have acne (No) with control did not have acne (No) (Mann-Whitney).
***P*-value[2]:** comparison between exposed participants who had acne (Yes) with control did not have acne (No) (Mann-Whitney).
***P*-value[3]:** comparison between exposed participants who had (Yes) with exposed participants who did not have acne (No) (Mann-Whitney).

Table 2. Association of serum levels of RANTES in SM-exposed and control groups with acne.

Study groups	(Diagnosis) Acne	RANTES						*P*-value[1]	*P*-value[2]	*P*-value[3]
		N	Median		Q3	Mean	SD			
Control	No	119	1313.00	0.000	1825	1394.06	848.70			
	Yes	5	915.70	0.290	1215	1204.60	852.56			
Exposed	No	322	842.65	651.70	1280	1125.29	849.06	<0.001		0.001
	Yes	23	1231.00	957.10	2099	1635.09	973.22		0.279	

The serum levels of RANTES in volunteers who had (Yes) and who did not have (No) acne were assessed and a comparison was undertaken between the control and exposed groups, as well as, within each groups.
***P*-value[1]:** comparison between exposed participants who did not have acne (No) with control did not have acne (No) (Mann–Whitney).
***P*-value[2]:** comparison between exposed participants who had acne (Yes) with control did not have acne (No) (Mann–Whitney).
***P*-value[3]:** comparison between exposed participants who had (Yes) with exposed participants who did not have acne (No) (Mann–Whitney).

Table 3. Association of serum levels of IL-1β in SM exposed and control groups with acne.

Study groups	(Diagnosis) Acne	IL-1β (Serum)						*P*-value[1]	*P*-value[2]	*P*-value[3]
		N	Median	Q1	Q3	Mean	SD			
Control	No	119	1.915	1.509	2.505	3.760	8.350			
	Yes	5	1.796	1.592	1.831	1.825	0.344			
Exposed	No	320	1.720	1.371	2.114	3.455	8.079	0.003		0.05
	Yes	23	1.935	1.644	2.692	5.077	12.655		0.723	

The serum levels of IL-1β in volunteers who had (Yes) and who did not have (No) acne were assessed and a comparison was undertaken between the control and exposed groups, as well as, within each groups.
***P*-value[1]:** comparison between exposed participants who did not have acne (No) with control did not have acne (No) (Mann-Whitney).
***P*-value[2]:** comparison between exposed participants who had acne (Yes) with control did not have acne (No) (Mann-Whitney).
***P*-value[3]:** comparison between exposed participants who had (Yes) with exposed participants who did not have acne (No) (Mann-Whitney).

Table 4. Association of serum levels of IL-1α in SM exposed and control groups with acne.

Study groups	(Diagnosis) Acne	IL-1α (Serum)						*P*-value[1]	*P*-value[2]	*P*-value[3]
		N	Median	Q1	Q3	Mean	SD			
Control	No	119	1.889	0.540	3.812	2.633	3.199			
	Yes	5	1.077	0.274	3.259	1.742	1.831			
Exposed	No	321	0.808	0.274	1.889	2.046	4.270	<0.001		0.776
	Yes	23	1.077	0.010	2.709	2.445	5.497		0.068	

The serum levels of IL-1α in volunteers who had (Yes) and who did not have (No) acne were assessed and a comparison was undertaken between the control and exposed groups, as well as, within each groups.
***P*-value[1]:** comparison between exposed participants who did not have acne (No) with control did not have acne (No) (Mann-Whitney).
***P*-value[2]:** comparison between exposed participants who had acne (Yes) with control did not have acne (No) (Mann-Whitney).
***P*-value[3]:** comparison between exposed participants who had (Yes) with exposed participants who did not have acne (No) (Mann-Whitney).

participants without acne disorder (1.72 pg/mL) was significantly ($P < 0.003$) lower than the matched non exposed control group (1.915 pg/mL). There was no significant difference between the individuals with acne and the control group without acne

Serum levels of IL-1α

As shown in Table 4, there was no significant difference between the level of IL-1α in SM-exposed group with and without acne.

The median of serum levels of IL-1α in the SM-exposed participants without acne disorder (0.808 pg/mL) was significantly ($P < 0.000$) lower than the matched non-exposed control group (1.889 pg/mL). There was no significant difference between the individuals with acne and the control group without acne.

Serum levels of IL-1Ra

As shown in Table 5, there was no significant difference between the level of IL-1Ra in SM-exposed group with acne and without acne.

The median of serum levels of IL-1Ra in the SM exposed participants with no acne disorder (25.88 pg/mL) was significantly ($P < 0.009$) lower than the matched non-exposed control group (33.6 pg/mL). There was no significant difference between the exposed individuals with acne and the control group without acne.

Serum levels of IL-12

As shown in Table 6, a somewhat significant ($P = 0.074$) difference in the level of IL-12 was seen between the exposed subgroups with acne (n = 23; median: 21.174) and without acne (n = 320; median: 10.624). There was no significant difference between the other subgroups.

Serum levels of IL-6

There was no significant difference in the serum level of IL-6,

Table 5. Association of serum levels of IL-1Ra in SM-exposed and control groups with acne.

Study groups	(Diagnosis) Acne	IL-1 Ra (Serum)						*P*-value[1]	*P*-value[2]	*P*-value[3]
		N	Median	Q1	Q3	Mean	SD			
Control	No	119	33.600	21.684	54.300	54.951	71.685			
	Yes	5	33.010	12.130	41.628	27.114	19.438			
Exposed	No	320	25.880	18.735	45.135	44.246	59.410	0.009		0.222
	Yes	23	34.680	15.880	51.968	54.063	81.313		0.956	

The serum levels of IL-1 Ra in volunteers who had (Yes) and who did not have (No) acne were assessed and a comparison was undertaken between the control and exposed groups, as well as, within each groups.
***P*-value[1]:** comparison between exposed participants who did not have acne (No) with control did not have acne (No) (Mann-Whitney).
***P*-value[2]:** comparison between exposed participants who had acne (Yes) with control did not have acne (No) (Mann-Whitney).
***P*-value[3]:** comparison between exposed participants who had (Yes) with exposed participants who did not have acne (No) (Mann-Whitney).

Table 6. Association of serum levels of IL-12 in SM-exposed and control groups with acne.

Study groups	(Diagnosis) Acne	IL-12 (Serum)						*P*-value[1]	*P*-value[2]	*P*-value[3]
		N	Median	Q1	Q3	Mean	SD			
Control	No	119	10.625	2.573	29.062	96.075	527.032			
	Yes	5	13.271	7.967	15.910	12.732	4.732			
Exposed	No	320	10.625	2.573	29.062	43.706	163.401	0.871		0.074
	Yes	23	21.174	7.967	34.327	318.199	1108.714		0.112	

The serum levels of IL-12 in volunteers who had (Yes) and who did not have (No) acne were assessed and a comparison was undertaken between the control and exposed groups, as well as, within each groups.
***P*-value[1]:** comparison between exposed participants who did not have acne (No) with control did not have acne (No) (Mann-Whitney).
***P*-value[2]:** comparison between exposed participants who had acne (Yes) with control did not have acne (No) (Mann-Whitney).
***P*-value[3]:** comparison between exposed participants who had (Yes) with exposed participants who did not have acne (No) (Mann-Whitney).

Table 7. Association of serum levels of IL-6 in SM-exposed and control groups with acne.

Study groups	(Diagnosis) Acne	IL-6 (Serum)						*P*-value[1]	*P*-value[2]	*P*-value[3]
		N	Median	Q1	Q3	Mean	SD			
Control	No	119	1.533	0.530	3.130	14.380	64.834			
	Yes	5	4.285	0.526	4.792	3.040	2.546			
Exposed	No	320	0.644	0.000	2.564	4.766	18.435	0.002		0.847
	Yes	23	0.339	0.066	1.992	27.167	125.093		0.033	

The serum levels of IL-6 in volunteers who had (Yes) and who did not have (No) acne were assessed and a comparison was undertaken between the control and exposed groups, as well as, within each groups.
***P*-value[1]:** comparison between exposed participants who did not have acne (No) with control did not have acne (No) (Mann–Whitney).
***P*-value[2]:** comparison between exposed participants who had acne (Yes) with control did not have acne (No) (Mann–Whitney).
***P*-value[3]:** comparison between exposed participants who had (Yes) with exposed participants who did not have acne (No) (Mann–Whitney).

between the exposed groups in the presence and absence of acne disorder (Table 7).

The median of serum levels of IL-6 in the SM-exposed participants with and without acne disorder (0.644 and 0.339 pg/mL) was significantly ($P = 0.002$ and $P = 0.033$ respectively) lower than the control group (1.533 pg/mL).

Discussion

SM, as an exogenous factor, is the most dangerous alkylating agent with multiple targets including DNA, proteins, and small molecules. As reported previously, DNA damage may lead to cytotoxity, trigger other changes, result in cellular dysfunction, cell death or disrupt tissue repair.[15,16] SM exposure can lead to impairment of both humoral and cellular immune responses.[17,18] SM up-regulates inflammatory mediators such as IL-1α, IL-1β, IL-6, IL-8, and TNF-α, and other cytokines in an acute phase of exposure.[15] We have recently reported a reduction in most of the inflammatory mediators such as IL-1α, IL-1β, IL-1Ra and TNF in an SM-exposed group of Sardasht-Iran Cohort Study (SICS)[19] twenty years after SM exposure.

In addition, the titration of serum levels of pro-inflammatory cytokines in SM exposed subjects with long-term dermatological complications has shown a decrease in these pro-inflammatory cytokines.[14]

Although decreased serum concentration of these pro-inflammatory cytokines was observed in patients with skin findings,[14] a different pattern of association between these pro-inflammatory cytokines and skin complaints was seen in a separate evaluation. Previously, we have reported a significant

association between enhancement of serum levels of MCP-1/CCL2 and the occurrence of cherry angioma in the SM-exposed group.[20] Also, there was a significant difference in the level IL-18 between the exposed subgroups with and without urticaria.[21] Also in a previous study, an association was reported between lack of cherry angioma and decrement of IL-8.[20]

The pathogenesis of acne appears be multifactorial and is not clearly understood. In this study, we examined the relationship between serum levels of pro-inflammatory cytokines (IL-1α, IL-1β, IL1Ra, IL-6, IL-8, IL-12 and RANTES) and the incidence of acne vulgaris in SM-exposed subjects. The number of patients with acne disorder was 24 (6.6%) in the SM-exposed group and 6 (4.7%) in the control group of SICS.[3] Acne prevalence is low because acne is usually recognized as an adolescent skin disorder. In our study, the average age of the control group was 41.8 ± 9.9 years which was matched to that of the exposed group (43.9 ± 10.8 years).[22] In this work, we evaluated serum levels of pro-inflammatory cytokines in SM-exposed individuals with acne compared to SM-exposed individuals without acne and normal controls. As shown in the results section, serum levels of IL-1β, IL-8, IL-12 and RANTES were higher in the exposed patients with acne than those of the exposed group without acne. There was no statistically significant difference between median serum levels of IL-6, IL-1α and IL-1Ra in SM-exposed groups with or without acne.

Except for the observed differences in serum levels of inflammatory cytokines between the SM-exposed war veterans with and without the acne disorder, the results obtained from comparing them with the acne-free control group are also significant. Almost all examined cytokines from the acne-free SM-exposed war veterans indicate a reduction against the control, while no significant difference was detected between the acne suffering SM-exposed veterans and the controls.

Consistent with these findings, relatively recent studies have indicated that serum IL-1b had a significant rise in obese and non-obese subjects with acne in comparison with acne-free subjects.[23] It has also been reported that *P. acnes* stimulates the production of pro-inflammatory cytokines, including IL-1β, IL-8, IL-12, and TNF-α via a toll-like receptor-2 (TLR2) dependent mechanism.[11,12] IFN-γ, IL-12p40 and IL-8 mRNA and protein production in PBMC from patients with acne had a significant increase compared to normal donors.[24] Furthermore, increased expression of cytokines and other inflammatory mediators such as IL-1a, IL-1b and IL-8 was observed in acne lesions *in vivo*.[25,26] Recent experiments show that *P. acnes* can induce IL-1b secretion via the NLRP3 inflammasome in human monocytes.[27] In contrast, one study reported that acne patients have higher serum concentrations of IL-10, but not inflammatory cytokines such as IL-1β, IL-6, IL-8, or IL-12p70, compared with healthy volunteers.[28]

We have previously reported that serum levels of IL-8 and IL-6 were significantly decreased in the SM-exposed participants compared to the control group.[29] Here, we found a significant increase in the serum level of IL-8 in exposed participants with acne compared to the exposed group without acne. However, the serum level of IL-8 is decreased in the SM-exposed without acne compared to the control group. Among the inflammatory mediators, IL-8 originally identified as neutrophil-activating peptide-1,[30] has recently shown that *P. acnes* modulates chemokine expression of keratinocytes and thereby has a decisive role in attracting neutrophils to the pilosebaceous unit.[31] Production of IL-8 by *P. acnes* is achieved through activation of the NF-kappa B.[11] Gene array expression profiling in acne lesions has revealed marked upregulation of genes, including IL-8, involved in inflammation and matrix remodeling.[32] There was no association between serum levels of IL-6 and acne in SM-exposed patients. Serum levels of IL-6 in SM-exposed participants with or without acne proved to have the same patterns seen in other SM exposed participants, which were previously reported by the same research group.[29]

According to our data, there is a somewhat significant increase in the serum level of IL-12 in exposed participants with acne compared to the exposed group without acne. IL-12 is the main pro-inflammatory cytokine which is secreted by monocytes in response to invading gram-positive organisms.[33]

We previously investigated the serum level of RANTES/CCL5 and found it to be significantly decreased in the SM-exposed population.[34] According to these data, we found a significantly elevated level of RANTES/CCL5 in the sera of SM-exposed patients with acne compared to SM-exposed veterans without acne. A significant association was seen between the decrement of serum levels of RANTES and the absence of acne in the SM-exposed group. In acne vulgaris, antimicrobial peptides (AMPs) could play a dual role; i.e., being protective by acting against *Propionibacterium acnes*, or being pro-inflammatory by acting as signaling molecules.[35] To our knowledge, there is no study on the association of serum level of RANTES with acne but Borovaya *et al.* reported that the relative cutaneous expression of several other AMPs such as RANTES did not show any significant change in acne patients compared to healthy controls.[35] Overall, further studies are recommended in this respect.

As mentioned, this study was part of the Sardasht Cohort Study and it was not conducted independently. Regarding the population size, we had to use the cohort protocol and the study was performed only on the population enrolled in the cohort. The small size of the sample and the heterogeneity of the group are among the limitations of this study which may consequently decline its analytic power.

In conclusion, we found a positive association between serum levels of IL-1β, IL-8, IL-12, RANTES and acne among the SM-exposed population. Furthermore, decreased levels of inflammatory cytokines in the SM-exposed group are related to the exposed group without acne, while the SM-exposed participants with acne did not show such alterations. The findings of decreased inflammatory cytokine levels in the acne-free SM-exposed group compared to the control group led to the assumption that SM exposure may create a certain disorganization, which could lead to skin complaints for some of the observed changes in the levels of SM-induced immunity mediators, which might propose a protective and compensatory function against disorders.

It seems likely that mustard gas-induced changes in cytokine patterns may differ in every individual, which may lead to different skin complaints. However, the confirmation of this hypothesis definitely requires further studies.

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Declaration of interest

The authors report no conflict of interest in this study.

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