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Biochemical and hematological findings of Halabja victims: 34 years after sulfur mustard exposure

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ABSTRACT

The city of Halabja situated in Kurdistan-Iraq faced a deadly attack using chemical warfare including the use of sulfur mustard (SM) in 1988. The survivors of this attack also faced the consequences of exposure to the toxic chemical SM in the form of multiple health complaints. The aim of this study is focused to gather data about the biochemical and hematological findings of Halabja victims who suffered from Sulfur Mustard (SM) exposure after completing 34 years of the attacks. A total of Twenty-five non-smoker patients (f: m19:6, mean age 59.2 years (range 35–85) and ten non-smokers control, healthy people (f: m 3:7, mean age 25.3 years (range 20–37) were interviewed and subjected to be tested. A purposive sampling strategy was adopted to recruit the study participants in August 2022. There were no significant differences between patients and controls regarding thyroid function markers. The levels of total protein and total albumin were significantly lower in the victims than in the controls (total protein: 7.67 ± 0.55 g/dL, $P < 0.05$, albumin: 4.30 ± 0.26 g/dL, $P < 0.01$). In addition, the serum high-density lipoprotein (HDL) was decreased significantly in patients compared to control groups (43.02 ± 8.15 mg/dL, $P < 0.01$). Moreover, triglyceride, low-density lipoprotein (LDL) and total cholesterol were not considerably increased in the patients. On the other hand, hematological parameters did not show a significant difference except for the mean corpuscular hemoglobin concentration (MCHC) level significantly lower in the victims than in the controls (33.48 ± 0.56 g/dL, $P < 0.01$). Finally, there were significant differences in total iron and ferritin levels in the groups. From this study, it was concluded that some of the victim's biochemical factors can be influenced owing to the long-term consequences of SM. From the similarity of functional test results of thyroid and hematology between groups, it is also stated that biochemical changes detected may be due to a patient's delayed respiratory complications.

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Introduction

A dreadful incident of massive war started in 1980 between Iran-Iraq and continued for eight years, Iraq used chemical weapons early and often. Finally, in March 1988, Iraq used chemical weapons during the war in Halabja city-Iraq against the Iranian soldiers that entered the city; unfortunately, it left long-term toxic effects on both the physical and psychological health of the victims in the city till now. Iraq's use of chemical weapons during the war reached a horrible escalation, months before the Iran-Iraq war termination, in 1988, with the notorious Anfal campaign against its Kurdish citizens having been done on another side. Anfal means "the Spoils" in Arabic as an 8-stage military, against Kurdish villagers living in Iraqi Kurdistan, a campaign which resulted in the conscious murder of approximately 50,000 and the slaughter of likely well over 100,000 Kurds (1, 2). Anfal was granted and done by the secretary general of the Northern Bureau of Iraq's Ba'ath Arab Socialist Party, named Ali Hassan al-Majid, who was also amongst the kins of former president Saddam Hussein. On March 29, 1987, Al-Masjid was made an authoritarian, because he was bestowed with power over all the state's agencies and authority, in northern Iraq, equal to that of a president. His rule and jurisdiction continued till April 23, 1989, (3, 4). Today, the Kurds know Al-Majid as "Ali Anfal" or "Ali Chemical," who was the surcharge of the Kurdish genocide (2).

In 1899, in Hague Convention, international law of prohibition on chemical weapon utilization during warfare was laid down (5). Nonetheless, Ali chemical, under his command on March 16, 1988, executed the largest chemical attack on Halabja city. In this brutal genocide, 5,000 people lost their lives instantaneously and 1000s of survivors are facing the miserable after-effects of this genocide in the form of never-ending life-long injuries to date (6). Iraqi forces used chemical weapons for some other towns and villages such as Gop-Tappa, Sewseenan, Sheikh Wassan, Dookan, Jaafaran, Mergapan's Mala Jaffakan and Baddenan Region (7, 8). A variety of chemical toxins were used in the Halabja attack, which majorly includes mustard gas (MS), sarin, tabun and VX. The latter three are known as strong nerve agents. Food, water sources, soil and animal populations are also deeply affected by the clutches of the toxins released from chemical weapons. (9-11). Unlike other nerve agents, SM is reported to possess high morbidity with low mortality. The Ministry of Martyrs and Anfal Affairs (MMAA) which comes under the Kurdistan Re-

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gional Government (KRG) documented in its unpublished report that in Kurdistan-Iraq, around 6,000 SM survivors are registered with more than one health issue (12). It is distressing to note that human security is under threat even today as similar occurrences of chemical attacks happen lately in the Syrian Civil war (13, 14).

According to the published research literature, the respiratory and ocular systems of the body are both severely affected by the short-term and long-term effects of SM. Long-term and delayed effects of SM on the neuropsychological system are also pronounced. SM also has profound consequences on the skin (7, 15-17). Patients from chemical weapons-exposed areas were interviewed in detail to assess their clinical history and sample collection was done to perform some laboratory tests. The organs of the human body that are reported targets of chemical weapons include the skin, eyes, bone marrow as well as the respiratory and neuromuscular systems (7, 18). Severe respiratory distress is noted in most of the survivors of SM exposure, presenting with complaints mostly associated with chronic bronchitis, emphysema, chronic obstructive pulmonary disease (COPD), bronchial and/or tracheal deformities, pulmonary fibrosis and frequently re-occurring pneumonia (12, 17, 19). Oxygen therapy was required in most of the survivors with a significant decrease in the victim's overall quality of life (1, 20). A close association of SM exposure has also been reported with psychiatric disorders (21). According to a study, when asked about the health status of the war survivors, the Iranian male war veterans reported reduced health-related quality of life (HRQOL) of the survivors versus the control group (22).

Experiencing the incident of war with massive and repeated war chemicals exposure inculcated the feeling of chronic fear among the survivors. This condition termed post-traumatic stress disorder (PTSD) further deteriorated the overall health status of the survivors (21, 23, 24).

The survivors of the Iraq chemical use in Halabja who presented with chronic health problems are registered as chemical weapons-exposed patients by the MMAA within the KRG. The government organization is responsible for the provision of donations or funds and other social benefits to the war victims. Symptoms severity and laboratory and radiological reports were used to ascertain the health status of the survivors by using a disability scale. A medical board mainly comprising pulmonologists, ophthalmologists, and dermatologists was also taken on board for sound clinical examination and medical reports interpretation. This study aims to evaluate the biochemical and hematological test findings in Halabja's victims positive for long-term respiratory symptoms after SM exposure. Our report here documents the use of a questionnaire methodology and blood sample collection for both affected individuals and the control group at the same time. Consequently, we proclaim that it is the first published scientific assessment of its kind, to investigate the health-related effects of chemical weapons on the Kurdish population in Halabja city via blood testing.

Materials and Methods

Patients and setting

In this study, a cross-sectional study design was adopted, after random sampling of 25 non-smoker survivors of SM exposure who were recruited from the Halabja Chemical Victims' Society; in Halabja, Iraq, the study duration was 3 months in the middle of 2022. All the victims have the respiratory disease and had at least one SM inhalation exposure during a chemical bombardment in 1988. The SM exposure documentation was contingent on the hospital of treatment of victims of chemical weapons in Halabja. Prescribed forms were used to collect and retain the demographic details, general physical examination, clinical history and other related information and other information. Only those subjects were enrolled and included in the study who met the criteria of documented SM exposure and associated diagnosis of chronic pulmonary lesions. Research assistants were trained to aid in the collection of baseline data by conducting well-structured face-to-face interviews. The following characteristics were considered as the complexity of respiratory syndromes: cough, dyspnea, hemoptysis, sputum and heartburn Gastroesophageal reflux disease (GERD) was diagnosed based on the history taking of the patients and physical clinical examination. Also, 10 healthy non-smokers, with no history of exposure to SM from the Halabja were randomly selected to include in a comparable control group. All the participants were asked for written and informed consent before the commencement of the study.

Blood samples

After overnight fasting, a brachial vein of the patient was identified to collect 10 mL venous blood samples for hematological and biochemical tests between 08:30 and 10:30 a.m. Sterile tubes with and without anticoagulants namely Ethylene diamine tetra acetic acid were used to collect blood samples for hematological and biochemical tests respectively. For biochemical assessment, the tubes were centrifuged at 3000 rpm for 5 minutes. The serum samples were then collected and kept at −70°C till further use. The serum collected was then used for the determination of biochemical parameters. Complete blood count including red blood cells count (RBC), white blood cells (WBC) count, hematocrit (Hct%), hemoglobin content (Hb), platelet (Plt) count, mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentration (MCHC), mean corpuscular volume (MCV), mean platelet volume (MPV), lymphocytes (LYM) count and granulocytes (GRA) count were measured using a hematology cell counter (Swelab alfa plus standard, Sweden) in the blood-related testing laboratory of the hospital for the treatment of victims of chemical weapons in Halabja. Thyroid function tests, lipid profile, total iron and ferritin were measured using an auto-analyzer (Cobas e411 and Cobas 6000 analyzer series) in the biochemical laboratory of the hospital of treating victims of chemical weapons in Halabja and Harem specialty diagnostic laboratory, Sulaymaniyah city, Iraq. This study was approved by the ethical committee of the College of Medicine, University of Sulaimani, with reference number 99 on September 04, 2022, in meeting number 1 (25, 26).

Biochemical analyses

Serum levels of T3, T4, TSH, and ferritin were measured by an assay kit that was purchased in Roche/Germany for the Cobas e analyzer (Cobas e411, Roche/Germany). Total cholesterol, HDL, LDL, TG, total protein, albumin, α 1-antitrypsin and total iron were measured by assay kit that was purchased in Roche/Germany for Cobas c systems

Table 1. Demographic data, clinical history, and physical examination data of 25 victims with delayed pulmonary complications.

Variable	Case Mean ± SD	Control Mean ± SD	P value
Age (year)	59.28 ± 11.32	25.3 ± 6.75	0.000 ***
Weight (kg)	72.68 ± 18.64	59.30 ± 13.31	0.047 **
Height (cm)	157.76 ± 8.17	161.8 ± 9.95	0.223
BMI (kg/cm^2)	29.16 ± 7.08	22.59 ± 4.69	0.011 *

(c 501 of the Cobas 6000 analyzer series, Roche/Germany) (27). Cobas is a fully automated, user-programmable analyzer designed to perform potentiometric and photometric assays in serum. The reagents in the kits have been set up into a non-separable, fixed ready-for-use assembly. Specialized reagent bar code technology is being used to automatically read the information required for specified functioning.

Statistical analysis

Quantitative data were represented as mean ± standard deviation. Necessary statistical analysis was performed using the statistical software namely Statistical Package for Social Sciences computer software (SPSS) version 20, Chicago, Illinois, USA. Independent samples t-test was the test of significance with 0.05 as the statistical significance level.

Results

General

25 non-smoker patients with delayed complications of SM exposure during Halabja were bombarded with chemical weapons in 1988 with ten non-smoker people as a control used in this study. 6 males and 19 females were included in the case group whereas the control group was comprised of 3 males and 7 females. The control group was not significantly different from the case group in gender and height while the age, weight and BMI showed significant differences. Demographic data of test and control groups are represented in Table 1.

All the survivors showed various signs and symptoms, with more subjective findings. The acute phase majorly has the characteristic episodes of symptoms triad, which includes cough, dyspnea and heartburn in 13, 18, and 12 patients respectively. Table 2 demonstrated the frequency distribution of respiratory syndromes, cough, dyspnea, hemoptysis, sputum and heartburn in the patients, derived using a questionnaire. The symptoms were not significantly different between both groups control and patient because the symptoms were not available in the control groups.

Table 2. Questionnaire-based frequency distribution data representing Dyspnea, cough, sputum, hemoptysis, and heartburn in the patients.

Symptom	Scale	Subjects (25 N)
Dyspnea	Acute	18
	Mild	5
	Few	2
	Never	0
Cough	Acute	13
	Mild	5
	Few	7
	Never	0
Sputum	Acute	8
	Mild	7
	Few	7
	Never	3
Hemoptysis	Acute	3
	Mild	5
	Few	8
	Never	9
Heartburn (GERD)	Acute	12
	Mild	5
	Few	6
	Never	2

Biochemical analysis

The basic values of biochemical serum parameters of the two study groups are shown in Table 3. No significant

Table 3. Comparison of biochemical findings between SM-exposed patients and controls.

	Case Mean ± SD	Control Mean ± SD	P value
T3 (nmol/L)	2.07 ± 0.38	2.26 ± 0.6	0.267
T4 (mol/L)	123.56 ± 20.39	130.61 ± 21.94	0.373
TSH (uIU/ml)	2.58 ± 1.92	2.36 ± 1.13	0.731
Total Cholesterol (mg/dL)	170.40 ± 53.83	160.30 ± 31.02	0.583
HDL (mg/dL)	43.02 ± 8.15	53.60 ± 10.4	0.003 **
LDL (mg/dL)	101.89 ± 44.15	90.00 ± 23.92	0.429
Triglyceride (mg/dL)	182.52 ± 107.95	133.40 ± 70.39	0.194
Total Protein (g/dL)	7.67 ± 0.55	8.13 ± 0.69	0.044 *
Albumin (g/dL)	4.30 ± 0.26	4.74 ± 0.57	0.004 **
α 1-antitrypsin (g/dL)	0.14 ± 0.01	0.14 ± 0.02	0.737
Total Iron (ug/dL)	92.48 ± 24.61	98.40 ± 33.85	0.569
Ferritin (ng/ml)	93.16 ± 81.22	80.57 ± 114.45	0.715

Table 4. Hematological parameters of control and case groups with their comparison.

Parameters	Case Mean ± SD	Control Mean ± SD	Normal ranges	P value
WBC (count 103/uL)	8.12 ± 2.01	8.15 ± 1.98	3.5–10	0.968
RBC (count 106/uL)	4.70 ± 0.49	4.62 ± 0.43	3.5–5.5	0.677
Hct (%)	40.18 ± 4.29	38.93 ± 3.68	35-55	0.424
Hb (g/dL)	13.43 ± 1.45	13.36 ± 1.33	11.5-16.5	0.894
PIt (count 105/uL)	2.44 ± 0.38	2.75 ± 0.58	1.3-4	0.077
MCH (pg)	28.62 ± 1.5	28.97 ± 2.47	25-35	0.615
MCHC (g/dL)	33.48 ± 0.56	34.34 ± 0.94	31-38	0.002 **
MCV (fL)	85.46 ± 3.86	84.21 ± 5.41	75-100	0.444
MPV (fL)	9.20 ± 0.81	9.27 ± 1.01	7.4-10.4	0.841
LYM (count 103/uL)	2.63 ± 0.77	2.34 ± 0.44	0.9-5	0.272
GRA (count 103/uL)	5.06 ± 1.64	5.45 ± 1.75	1.2-8	0.547
MID (count 103/uL)	0.42 ± 0.24	0.36 ± 0.36	0.1-1.5	0.578

differences were detected in the results of serum blood T3, T4 and TSH between the case and control groups. Table 3 provides a distinct comparison between the lipid profiles of the case and control groups. Significantly higher levels of HDL in the control group and significantly lower levels of serum albumin and total protein in the case group were observed. No significant change (increase) was observed in the levels of serum total cholesterol, LDL and TG in the case group in comparison with the control group. Finally, for serum α 1-antitrypsin level, total iron and ferritin levels in the case group in comparison with the control group were observed which was non-significant.

Hematological parameters

The hematological characters of 25 patients and 10 control subjects are shown in Table 4. Except for the MCHC, the results of the rest of the parameters did not show any significant difference between groups.

Discussion

Irrespective of the international restrictions on the utilization of SM and related toxic chemical agents, it is still synthesized, stored and illegally utilized massively in different regions of the world (5). The objective of this study was to determine the delayed complications associated with SM exposure in the Halabja victims who were living in that city. SM produces both short-term and long-term effects on different organs of the body. Respiratory complications are the main cause of long-term disability among SM-exposed victims (28). Although the majority of thyroid tests were normal in our study without significant differences, whereas according to a recent study that has done in Sardasht-Iran for exposed cases with SM showed the mean only of T3 concentration was significantly higher in the exposed than the control group (29). In this study, a significant decrease was observed in the concentrations of serum albumin and total protein in the case group. Similar results were reported previously in studies where a significant decrease in total protein and albumin levels was observed in the population exposed to SM in Iranian veterans (30, 31). Reduced de-novo synthesis by the liver, loss of kidney/s, chronic inflammation and undernourishment are the major reasons for hypoalbuminemia (32). Direct plasma protein loss due to compromised kidneys (as in nephrotic syndrome) or less synthesis due to liver pathology is also directly responsible for reduced albumin concentration (33, 34). Significantly decreased albumin concentration in the case group may be the result of the high frequency of respiratory infections present in survivors rather than the direct toxic effects of SM on the liver. Serum albumin can easily be used as a marker of inflammation, it is a negative acute-phase protein (35). The inflammation process results in cytokines outflow including interleukin-6 (IL-6), which is operated through specific hepatic receptors to halt albumin synthesis (35). Also, IL-6 stimulates lung fibroblast proliferation through a positive autocrine feedback mechanism (36, 37).

In the present study, reduced levels of serum total protein and albumin have been observed in the victims' group which can be due to the compromised kidney function. On another hand, the α 1-antitrypsin level was not significantly different between the opposite groups. However, based on the research done by Shohrati and his colleagues, a significant reduction in α 1-antitrypsin level was claimed in the patient group than the control groups (38). The results of the defined thyroid tests of the patients remained statistically unchanged. Our findings revealed about lipid profiles were supported by the previous study that has done in Khorasan veterans in Iran (30). In this study, serum TG, LDL and total cholesterol of the patients were not significantly higher than in the control group while HDL level, which is known as good cholesterol, was significantly lower in the exposed than in the control group. This may be owing to the reduced daily hours of physical activity among the veterans in comparison to the control group which shows a relationship between serum lipid profile level and hours of physical activity (39-41). The significant decrease in the level of MCHC may be due to the already existing chronic respiratory problems of the group. In this study, no evidence of anemia was found in our patients. The average number of red blood cells and hemoglobin of victims compared with the controls were not significantly different, with slightly higher values in the case group when compared with the control group. White blood cells, lymphocytes and granulocytes did not show any clinically meaningful variation between groups. The rise in erythroid cells and hemoglobin concentration may be the result of chronic obstructive pulmonary disorder or other respiratory diseases in these patients (18, 42).

From the findings of this research study, no direct long-term toxic effects on thyroid gland functionality are depic-

ted. Decreased albumin, total protein and MCHC levels might be a consequence of secondary to delayed respiratory complications already present chronically in patients. Low daily hours of physical activity could be the reason behind the elevated levels of serum lipids among the survivors. Further studies are necessitated to identify and better understand the long-lasting toxic effects of SM on surviving victims.

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Competing interests
The authors declare that they have no competing interests.

Author contributions
The author conceived the study idea, supervised and carried out all of the lab work, drafted the manuscript, edited the manuscript and approved the final manuscript.

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