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CLINICAL PRESENTATION OF CHEMICAL WARFARE INJURIES IN CHILDREN AND TEENAGERS

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ABSTRACT

Clinical manifestations of sixteen children and teenagers exposed to chemical warfare in Halabje are presented. 15 patients complained of burning of skin. Dry coughing was present in 13 subjects. The most frequent signs were conjunctivitis, skin erythema, edema of the eyelids, hyperpigmentation, ulceration, erosion, dyspnea, closure of the eyes, blisters, edema of the skin, and crepitation in both lungs, in decreasing order of frequency. Two subjects had severe fatal leukopenia and anemia and three showed a transient leukopenia. Four of sixteen died of bone marrow hypoplasia, sepsis and respiratory distress. This report again reminds need for an urgent international agreement to effectively ban the use of chemical weapons.
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INTRODUCTION

Chemical weapons were extensively used during the First World War and their side effects on the eyes, skin, gastrointestinal, respiratory and hematological systems of adult men have been known.[1]

Although the use of chemical warfare was banned by the Geneva Protocol in 1925,[2] research on chemical warfare agents, their mode of delivery, and antidotes continued in the intervening 60 years.[3]

The use of chemical war agents by the Iraqi regime against Iranian soldiers was reported[4] and condemned[5] by the United Nations Security Council; however their use continued and on March 17, 1988 extensive chemical weapons were delivered in the city of Halabja.[6] Many of those who survived were brought to Iranian Hospitals. We had opportunity to receive sixteen children and teenager inhibitants of Halabja in our hospital; the clinical signs and symptoms and some laboratory studies in these children and teenagers are the subject of this report.

PATIENTS AND METHODS

During the Iran-Iraq conflict following the employment of chemical warfare which was reported repeatedly by Iran, confirmed by the scientists,[7,8] and condemned by the United Nations,[5] a scientific committee was formed by Iranian Ministry of Health in order to concord and guide the research activities in people injured by chemical warfare and to advise the best treatment modalities. A special admitting form, including check list for vital signs and 89 symptoms and signs related to chemical injury was adopted, and distributed to the university hospitals. House officers were asked to complete the form on days 1,2,3,5,7,10 and 14 after admission.

Medical records of 16 children who were admitted to the Mofid Medical Center after they were injured by chemical warfare in Halabja were studied. The children were exposed to chemical agents at 5:30 pm on March 17, 1988 and they were brought to the hospital one to twenty days later. Clinical symptoms and signs of the victims and chemical determination by special kits showed that nerve agents, cyanide and vesicants were used. They were 12 girls aged five months to 12 years and four boys aged three to 11 years. On the day of admission, CBC, urinalysis and serum determinations of glucose, urea, calcium, sodium, potassium, and arterial blood gases had been performed. Since many of the patients had recieved intravenous dextrose solution and showed increased FBS, we had to discard the results of blood glucose. Serial CBC determina-

Table I. Admission vital signs in children injured with vesicants.

No:	Day (s) After exposure	Age	Sex	Pulse rate Per minute	Respiratory rate per minute	Temp. erature (C)	Remarks
1	1	8	M	120	42	40.0	Died
2	1	12	F	106	36	40.0	Died
3	2	5	F	120	36	39.5	
4	3	0.4	F	140	30	39.0	Died
5	3	10	F	140	40	38.0	
6	3	10	M	110	30	38.0	
7	4	9	F	100	36	37.5	
8	8	3	M	140	60	39.5	Died
9	9	5	F	120	36	38.5	
10	10	6	F	110	37	37.5	
11	10	3	F	110	36	38.0	
12	10	3	F	120	36	37.0	
13	10	9	M	90	24	37.5	
14	12	4	F	134	40	38.0	
15	12	9	F	100	20	37.0	
16	20	5	F	140	20	36.8	

tions were performed every three to five days in those who survived.

Table II. Clinical findings in 16 children injured with vesicants.

Sign	Number	Percent
Ocular:		
Conjunctivitis	15	94
Edema of the eyelids	13	81
Closure of the eyes	10	63
Keratitis	6	38
Blepharospasm	4	25
Corneal ulcer	3	19
Chemosis	1	6
Cutaneous:		
Erythema	15	94
Hyperpigmentation	12	75
Ulceration	11	69
Erosion	10	63
Blister	9	56
Edema of the skin	8	50
Vesicle	5	31
Hypopigmentation	2	13
Respiratory:		
Dyspnea	10	63
Crepitation	8	50
Wheezing	4	25

RESULTS

Age, sex and admission vital signs are shown in Table I. There were 4 boys aged three to 10 years and 12 girls aged five months to 12 years. Four of 16 (25%) died two to 21 days after exposure. All four patients had serious involvement of skin, eyes and respiratory system.

Case 1: An 8-year-old boy was admitted one day after exposure. He was febrile (40°C), severely agitated, delirious and somnolent. BP was 110/70 mmHg, PR 120 per minute and respiratory rate 42 per minute. Dermatological involvement including erythema, erosions, vesicles, blisters, ulcerations, and edema was obvious in 35% of the skin. He was suffering from conjunctivitis and palpebral edema. Patient was dyspneic, using his accessory respiratory muscles and in auscultation there was wheezing and crepitation throughout both lungs. WBC was 9900/mm^3 with 90% neutrophils. Blood urea was 25 mg/dl, calcium 7.3 mg/dl, sodium 139 and potassium 4.1 mEq/l. Arterial pH was 7.30, PCO_2 31, PO_2 65 and HCO_3 15.1. Chest X ray showed infiltration in both lungs. He died, despite all supportive measures, 24 hr after admission, two days after exposure to chemical warfare.

Case 2: A 12-year-old girl was admitted one day after exposure. She was febrile (40°C), agitated and somnolent. BP was 90/40mmHg, PR was 106 and respiratory rate 36 per minute. Serious dermatological (45%), ocular and respiratory involvement was present, as described in case 1. On admission, hematocrit was 50%, WBC 20, 000/mm^3 with 93% neutrophils, blood urea 51 mg/dl, calcium 8.3 mg/dl, sodium 133 and potassium 5.8 mEq/l. pH was 7.27, P CO_2 14, PO_2 83 and HCO_3 6.3. Chest X ray showed bilateral diffuse infiltration. She developed bone marrow hypoplasia in a few days. Five days after admission, the hematocrit had dropped to 23%, WBC had fallen to 2100 mm^3 with 82% neutrophils and 18% lymphocytes. She died seven days after exposure to mustards, despite antibiotic therapy and all supportive measures. Blood cultures drawn on the fifth day of admission grew coagulase positive staphylococci.

Case 4: A five-month-old girl was brought to the hospital three days after exposure to chemical warfare, with severe signs of cutaneous, ocular, and repiratory system involvement, described in case 1. Temperature was 39°C, PR 140 and respiratory rate 30 per minute. Blood urea was 22 mg/dl, calcium 8.2 mg/dl, sodium 136 and potassium 4.2 mEq/l. pH was 7.37, PCO_2 19, PO_2 74 and HCO_3 9.4. Chest X-ray showed slight patchy infiltrates in both lungs. The hemoglobin was 8.9 gm%, hematocrit 28%, WBC 2200/mm_3 with 90% polymorphonuclears and 10% lymphocytes. Despite antibotic therapy and supportive measures, the patient died on the third day of admission, six days following injury.

Case 8: A three-year-old boy was brought to the hospital eight days after he was injured by chemical warfare. He was febrile (39.5°C), tachycardic (140 per minute) and tachypneic (60 per minute). His cutaneous

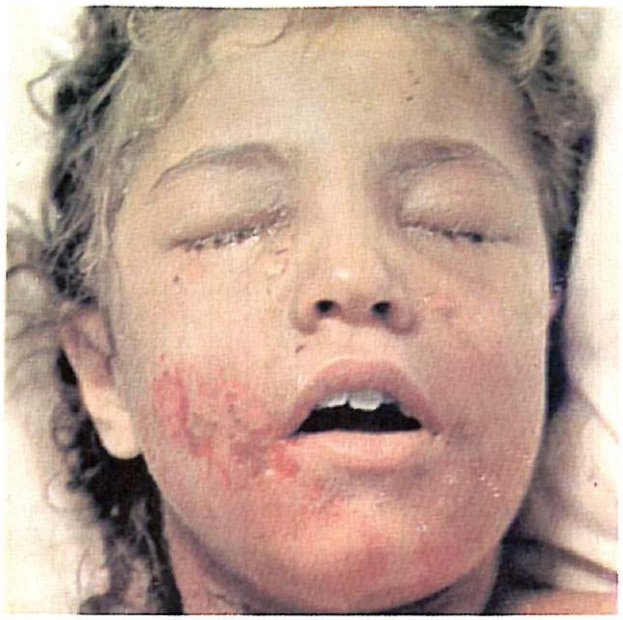

Figure 1. Severe photophobia, lacrimation, and facial skin lesions in a girl following exposure to mustard gas.

lesions were milder than other cases but up to 45% of the skin had erythema and edema. The ocular and respiratory symptoms were as described in case 1. Except for mild anemia, his laboratory workup was unremarkable. Chest X-ray showed bilateral hilar congestion and consolidation.

His fever continued despite antibiotic therapy and on the 18th day after exposure he developed leukocytosis with 82% polymorphonuclears. His respiratory distress became worse and he died 21 days after exposure to chemical warfare.

As shown in Table I, only three of 16 patients had body temperature below 37.5%. Many had tachycardia and tachypnea.

All sixteen patients complained of some ocular and cutaneous involvement. Burning of the eyes, lacrimation and photophobia were present in 15 (94%) subjects. Pain and burning of the involved skin was also reported by 15 (94%) patients. 13 subjects (81%) complained of dry coughing. Less frequent complaints were blurred vision, itching, sore throat, burning of upper resipiratory tract, sneezing, nasal secretion, dyspnea, feeling of suffocation and change in the voice.

Clinical findings related to skin, eyes and respiratory system dominated the clinical picture (Table II). Fifteen of 16 patients had signs of ocular and cutaneous involvement. More than two thirds of the patients demonstrated conjunctivitis, edema of the eyelids and skin erythema (Fig. 1). Half of the subjects showed eight more signs including hyperpigmentation, ulceration, erosion, blister, edema of the skin, closure of the eyes, dyspnea and crepitation in both lungs. Keratitis, blepharospasm, corneal ulcer, chemosis, appearance of vesicles and hypopigmentation, hoarseness and wheezing in the lungs were less frequently observed.

The results of serial CBC determinations are shown in Table III. In only two patients (cases 2 & 4) hematocrit was below 30%; both patients had severe leukopenia (2100 and 2200/mm^3 respectively) and died within one week after injury. In three other cases (5,6, & 7), there was transient decrease in WBC with subsequent recovery. In case 7, WBC fell from 10300 to 2600 two weeks after exposure, but increased after 5 days. Cases 5 and 6 showed a mild transient decrease in WBC from 8000 and 7200 to 4200 and 3400 respectively, with subsequent recovery after a few days. Occasional increases in WBC were mainly due to accompanying infection. In those who had decrease in hematocrit and/or WBC, this usually occurred in the first two weeks. In fact the lowest mean hemoglobin, hematocrit, WBC and neutrophil count was observed in the sixth to 10th day samples.

The results of some blood constituents and the blood gases on the first day of admission to the hospital are shown in Table IV. BUN was elevated in six cases, three of whom died. Subsequent BUN determination in three other patients had shown the return of BUN to normal values. Serum creatinine and other renal function tests could not be found in the charts. Serum calcium was below 8 mg/dl in three cases and sodium was below 130 mEq/l in only one case. Serum potassium was above 5 mEq/l in two cases. Of 14 patients who had blood gas determination, simple metabolic acidosis was evident in six (43%; cases 1,4,6,7,10 and 12), mixed metabolic acidosis and respiratory alkalosis in four (28%; cases 2,5,9 and 14) and simple respiratory alkalosis in two (cases 3 and 15). Case 11 had mixed metabolic and respiratory acidosis and case 13 showed mixed metabolic alkalosis and respiratory acidosis.

DISCUSSION

This study demonstrates the clinical and biochemical alterations in children and teenagers exposed to chemical warfare in Halabja. The number of substances that have been examined as candidate chemical weapons exceeds hundreds of thousands; extensive search for the synthesis of chemical warfare agents was launched in the second half of the ninteenth and the first two decades of the twentieth centuries, which led to the development and use of various categories of chemical weapons during the First World War. Of the most frequently used lethal chemical warfare, the nerve gases and cyanides are most rapidly and completely absorbed into the circulation through the lungs, causing sudden loss of consciousness and prompt death, if used in high doses.[9] With smaller but still lethal

Table III. Hemoglobin, hematocrit and white blood cell counts in children injured with vesicants.

est	Hgb (g%)					Hct (%)					W.B.C. (mm^3)					Neutrophil (%)					Lymphocyte (%)				
	1-5	6-10	11-15	16-20	> 20	1-5	6-10	11-15	16-20	> 20	1-5	6-10	11-15	16-20	> 20	1-5	6-10	11-15	16-20	> 20	1-5	6-10	11-15	16-20	> 20
No:																									
1	13.4					42					9900					90					6				
2	15.9	7.1				50	23				2000	2100				93	82				3	18			
3	10.7		11.2	11.5		34		40	41		7100		3500	7900		99		48	70		21		52	30	
4	8.9					28					2200					90					10				
5	10.7	10.0	10.4		11.3	33	31	35		39	8000	4200	5500		9800	97	73	68		82	2	22	32		18
6	13.2		12.1	12.6	11.1	41		41	41	37	7200		3400	6300	10000	90		81	79	81	10		19	21	18
7	11.8		10.0	12.4	13.0	37		38	42	45	10300		2600	5600	11600	90		26		74	8		74	41	23
8		10.2	11.3	11.7	10.0		33	40	42	42		5800	5600	15300	9200		68	72	82	93		32	26	12	7
9		10.3	10.6	9.8			37	37	33			7400	8000	5000			79	86	74			12	14	26	
10		11.3	11.6				39	41				6100	7600				63	70				30	25		
11		11.9	11.2				39	39				8100	8400				46	55				45	42		
12		11.2	11.5				38	41				9200	15900				59	79				33	18		
13		11.7	10.5	10.9	10.8		38	37	38	39		5200	4400	4500	7700		59	62	68	60		32	32	32	40
14			10.7	11.0	12.1			36	39	44			10000	7400	11500			48	71	75			29	29	21
15			11.8	11.8	11.2			40	40	44			22300	10000	9600			89	71	71			11	25	25
16				12.8					51					8100					75					25	

doses, each of two groups of agents will produce special symptoms and signs, and result in death within several minutes to a few hours. However, when the dose of chemical agent is not high enough to cause death within the first 24 hours after exposure, often complete recovery occurs; and subjects do not require hospitalization.

The vesicants, or blister agents, including mustard gas are general tissue irritants with an additional systemic action. Mustard gas (Yperite, Lost: bis (2-chloroethyl sulfide) may occasionally cause acute toxic effects only at supralethal dosages. However, most subjects exposed to mustard gas do not experience any effect immediately following exposure, and many will disclose manifestations minutes or hours after the injury, when the maximum exposure to the mustard gas has occurred. Generally, the first symptoms occur between a half and several hours after exposure, succeeded by the gradual appearance of upper respiratory tract, ocular and dermatological symptoms and signs in the following hours. At the end of 24 hours all symptoms and signs are evident.

From the foregoing discussion, it is clear that although nerve gases, cyanides and mustard gas were used in Halabja, our patients who had survived the first 24 hours after exposure were contaminated mostly with mustard gas. In fact all 16 children and teenagers showed the typical manifestations related to mustard gas injury.

Clinical presentation of mustard gas injury has been cited before,[1,9] and recently reported in many hundreds of Iranian casualties during the Iran-Iraq war.[10-12] However except for a report on clinical aspects of accidental dichloroethyl sulfide poisoning in four children,[13] we were unable to find any report of the effects of mustard gas on the children and teenagers in the literature. Our clinical findings of ocular, dermal and respiratory manifestations are in accordance with those found by Balali in Iranian fighters five days after exposure [10](Table V), and almost similar percentage of major symptoms have been observed in children and teenagers. The frequency of occurrence of major symptoms in all those who are exposed to mustard gas in the battlefield is probably much less, since only severe and moderate cases are admitted to the hospital and others are managed in outpatient services. In fact, in a report from Shaheed Chamran University of Medical Sciences, Ahvaz, Iran, about 25 Iranian fighters injured during the "Valfajr 8 Operations", only 44% had remarkable ocular and cutaneous findings and 36% had respiratory involvement.[14]

Among sixteen children and teenagers studied in this report, two (12%) had severe leukopenia and anemia, most probably due to bone marrow hypoplasia and three (19%) had only transient leukopenia. Both severe fatal[11,15-17] and transient[12] leukopenia has been reported after exposure to mustard gas. It has been suggested that no patient can survive with a WBC count less than $1400/mm^3$.[15]

The results of blood chemistry and blood gases were not conclusive, since serial determinations could not be found in the charts and adequate renal and respiratory function tests could not to be found in the charts. However, one can say that many patients suffered from hypoxemia and some from renal failure.

The frequency of lethal outcome from mustard gas exposure is variable and depends on the amount of gas

Table IV. Serum concentrations of urea, calcium, sodium and potassium and arterial blood gases in children injured with vesicants.

No:	Day (After) exposure	B.U.N (mg/dl)	Calcium (mg/dl)	Na (mEq/l)	K (mEq/l)	PH	PCO_2	PO_2	HCO_3
1	1	25	7/3	139	4.1	7.30	31	65	15.1
2	1	51	8.3	133	5.8	7.27	14	83	6.3
3	2	7	7.6	127	4.0	7.45	28	68	18.7
4	3	22	8.2	136	4.2	7.37	19	74	9.4
5	3	18	8.2	137	4.8	7.36	18	79	10.0
6	3	61	9.0	137	4.9	7.33	22	69	11.4
7	4	25	8.8	136	4.7	7.31	24	52	11.9
8	8	7	9.4	130	3.7	-	-	-	-
9	9	8	9.6	140	3.9	7.40	29	81	17.8
10	10	13	9.7	136	4.1	7.35	27	95	14.6
11	10	12	9.7	136	5.1	7.26	46	107	20.3
12	10	12	9.6	133	4.6	7.22	24	111	9.4
13	10	10	8.5	135	4.3	7.52	61	126	48.2
14	12	14	8.2	136	4.4	7.41	24	78	14.8
15	12	9	7.3	134	4.4	7.43	31	78	20.0
16	20	28	8.8	137	4.1	-	-	-	-

used, the employment of protective measures, immediate escape from the field, and availability and promptness of supportive medical and nursing measures. One of every four subjects in the present study died of bone marrow hypoplasia, sepsis and respiratory failure (two, one and one patients respectively). The mortality rate in some combatants referred to Ahvaz hospitals was four in 14 in the "Kheibar" Operation.[14] Other larger series have not reported the rate of mortality.[10,12,16]

For the surviving children and teenagers, close follow up must be performed for years; since both mutagenicity and carcinogenicity of chemical weapons, especially mustard compounds, have been reported.[18,19]

Sulfur mustard is an alkylating agent causing covalent linkages with various nucleophilic substances. Its cytotoxic effect is directly related to the alkylation of components of DNA, espically the 7-nitrogen atom of guanine.[20] Mustard preparations cross-link the twin strands of the DNA macromolecule, resulting in prevention of DNA replication.[21]

Chemical weapons were not used in the Second World War, although both sides had developed new generations of agents. This led to the hopes that chemical weapons would never be used. In fact Torald Stollmann in his Textbook of Pharmacology published in 1957 wrote: "Its importance (mustard gas) is now past history, and may perhaps never be revived."[22]

However, research on chemical warfare continued by the British and Americans in 1950's and 1960's, resulting in the discovery of new chemical war agents.[3] The massive use of herbicides and defoliants by the American army in the Vietnam war (1961-72)[23] opened a new era in the use of these devastating agents.[24] The continuous use of all kinds of chemical weapons by the Iraqi army during the Iran-Iraq conflict,[4-8] and extension of chemical bombing from battlefield to cities and towns requires serious concern and immediate actions in order to save our children and future generations.

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