Health Effects Associated With Long-Term Occupational Exposure of Employees of a Chlor-Alkali Plant to Mercury

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This study aimed to evaluate possible health effects associated with long-term occupational exposure to low levels of mercury vapors. Forty-six subjects exposed to mercury and 65 healthy unexposed employees were studied. The subjects were administered a questionnaire on experienced symptoms and underwent clinical examinations as well as routine biochemical tests. Atmospheric and urinary concentrations of mercury were measured, too. Environmental concentrations of mercury were estimated to be $3.97 \pm 6.28 \,\mu g/m^3$ and urinary concentrations of mercury in exposed and referent groups were 34.30 ± 26.77 and $10.15 \pm 3.82 \,\mu g/m^3$, respectively. Additionally, symptoms such as somatic fatigue, anorexia, loss of memory, erethism, blurred vision and teeth problems were significantly more common among exposed individuals. These observations indicate that occupational exposure to mercury vapors, even at low levels, is likely to be associated with neurological and psychological symptoms.

chlor-alkali plant mercury exposure neurological symptoms psychological symptoms

1. INTRODUCTION

Mercury is a metallic element that occurs naturally in the environment. There are three forms of mercury and its compounds: elemental, inorganic and organic. Elemental mercury is the main form of mercury released in a natural process into the air as a vapor. Exposure to elemental mercury of the

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general population and in occupational settings is primarily through inhalation of its vapor [1]. Occupational exposure to mercury basically occurs in chlor-alkali plants of petrochemical industry, fluorescent light bulb manufacturing factories, glass blowing industries, amalgam fillings in dental clinics, small-scale gold mining and production of vinyl chloride monomer [2, 3]. At present, mercury finds its largest use in artisan work and small-scale gold mining [3].

The chlor-alkali industry is also a major source of industrial mercury pollution [4]. Electrolysis cells are formed of mercury and titanium as cathode and anode that, under the influence of high-intensity direct electric current, analyze aqueous solution of sodium chlorine and produce chlorine gas, hydrogen and caustic soda. Mercury in the cells is constantly circulated with a pump and may leak during electrolysis and maintenance. Mercury leakage exposes workers to the vapor of this metal [5].

The effects of short-term, high-level exposure to the various forms of mercury are wellestablished although the consequences of longterm, low-level exposure are not as yet fully characterized. The type of mercury is an important determinant of toxicokinetic behavior of this element. In human, mercury vapor (Hg^0) is readily absorbed through the respiratory tract (~80%), only poorly by the gastrointestinal tract (~0.01%) and only to a limited extent via the skin (0.024 ng Hg/cm² skin per 1 mg Hg/m³ present in air) [6].

The central nervous system is considered the critical organ for mercury toxicity [6, 7, 8, 9, 10, 11, 12, 13, 14, 15]. A wide variety of respiratory, cardiovascular, gastrointestinal, reproductive, hepatic, renal, thyroid, hematologic, dermal, musculoskeletal, immunologic, sensory and genotoxic disorders has been associated with mercury exposure. Symptoms such as irritability, psychological change, weakness, cognitive disorders, shyness, erethism, depression, insomnia, polyneuropathy, paresthesia, emotional lability, personality changes, headache, weakness, blurred vision, dysarthria, speech impairment, slowed mental response and unsteady gait and behavioral changes, loss of weight, loss of appetite, gingi-

vitis [6, 16], impaired memory [13, 14, 15, 16, 17, 18], sleep disorders [14, 15, 16, 17], fatigue and confusion [13, 14, 15, 16, 17], tremor [11, 15] have been noted in mercury poisoning. Additionally, depression along with negative self-concept have been noted among a group of miners with past occupational elemental mercury exposure [19]. Short-term exposure to mercury has been reported to be accompanied by increased blood pressure [6], adverse effects on oral health (i.e., oral mucosa ulceration), inflammation of the gums and loosening or sudden falling out of teeth [20].

In studies conducted at chlor-alkali plants, neurological effects of mercury exposure have been investigated [7, 8, 10, 11, 12, 13, 14, 15, 17, 18]. Some studies reported significant increases in neuropsychological symptoms [12, 13, 14, 15, 17, 18]. Conversely, other studies found no correlation between mercury exposure and symptoms [7, 8]. Comparing these studies is difficult due to differences in the study design, exposure scenarios and length of exposure.

In recent years, there has been concern regarding health effects of mercury exposure among employees of a local chlor-alkali plant in Iran. Visiting the plant and assessing workers' occupational exposure with a mercury vapor indicator, the authors found that the workers were exposed to high levels of mercury, exceeding the threshold limit value (TLV). Following this observation, the employer was asked to improve the ventilation system and to maintain a clean area by washing the site thoroughly on a daily basis with a concentrated solution of sodium thiosulphate. The current study was designed and conducted after these interventions to examine the effectiveness of the measures and to re-evaluate the workers' health through measuring their urinary mercury concentration, neurobehavioral responses and conducting biochemical tests. The study also aimed to determine the workers' status of occupationally exposed to mercury.

2. MATERIALS AND METHODS

2.1. Subjects

This cross-sectional study was carried out in a local chlor-alkali plant. The study population consisted of 46 male workers of the chlor-alkali plant (exposed group) and 65 randomly selected healthy workers from the same industry without a history of occupational exposure to mercury (referent group). The study was conducted in accordance with the Helsinki Declaration [21]. None of the exposed or referent subjects had a history of previous neuropsychological disorders (pre-existing medical conditions) or inherited disorders at the commencement of their employment.

2.2. Variables

2.2.1 Demographic characteristics and symptoms

For all participants a two-section questionnaire was completed. The first section covered demographic variables (age, gender, height, weight, marital status and length of exposure/employment). The second one concerned symptoms of mercury intoxication: physical and mental fatigue, loss of appetite, writing difficulties, irritability, insomnia, anxiety, anorexia, etc. The questionnaire was completed by interviewing the subjects.

2.2.2 Physical examination and laboratory tests

All participants were examined by a physician (as a part of their periodic medical examinations). Where needed, they were referred to a relevant specialist. Blood samples were taken from all participants. For the complete blood count and kidney and liver function tests, samples were sent to a diagnostic laboratory affiliated to Shiraz University of Medical Science. The complete blood count test was done automatically with a k21 cell counter (Sysmex, Japan). Moreover, serum activity of liver enzymes (alanine amino transferase and aspartate amino transferase), alkaline phosphatase as well as bilirubin and blood urea nitrogen were measured with standard methods on a fee-for-service basis.

2.2.3 Measurement of environmental mercury concentrations

The concentration of mercury in the ambient air of the chlor-alkali plant was measured with an HG monitor 3000 mercury analyzer (Seefelder Messtechnic, Germany). This compact fixedwavelength UV photometer operates on the principle of atomic absorption spectroscopy. Using the built-in flow pump, air passes through an optical cuvette in the instrument and real-time values are displayed continuously. In addition to instantaneous concentrations, the device is also programmable for 90-m sampling and shows the mean concentration during this period, which was the basis for the measurements in this study. The detection limit and the measurement uncertainty of the instrument are $0.5 \,\mu\text{g/m}^3$ and under 0.5% of measuring range, respectively.

2.2.4 Measurement of urinary mercury concentration

Twenty-four-hour urine samples were collected from the subjects [22]. Then the samples were sent to the laboratory while the necessary precautions were considered. Mercury analysis was carried out with cold vapor atomic absorption spectrophotometry with a Chemtech AA spectrophotometer (model CTA 3000, UK). Urinary mercury levels were reported as micrograms per cubic decimeter of urine.

2.3 Data Analysis and Statistical Procedures

 χ^2 test was used to compare the frequency of symptoms among both groups. Fisher's exact test was used when numbers were too small for χ^2 test to be valid. Odds ratios and 95% confidence intervals were calculated. Independent sample *t* test and Mann–Whitney *U* test were used to compare the mean and median of quantitative data of both groups. Multivariate logistic regression analysis was used to examine the adjusted effect of mercury exposure on the occurrence of various symptoms and disorders. Two-tailed p values were reported throughout (p < .05 was considered significant). Statistical analyses were done with SPSS version 11.5.

3. RESULTS

The mean age of the exposed workers was 35.09 ± 9.90 years and that of the referent group was 41.83 ± 5.91 years. The mean length of exposure/employment of the exposed individuals and referent subjects was 10.61 ± 10.90 and 17.76 ± 5.82 years, respectively. These data indicate that unexposed subjects were, to some extent, older than exposed individuals; the differ-

ences were statistically significant (p = .001). The mean values of urinary mercury for exposed and referent workers were 34.3 ± 26.77 and $10.15 \pm 3.82 \,\mu\text{g/dm}^3$, respectively; the difference was statistically significant (p < .001) (Table 1).

The mean value of urinary mercury concentration for 4.3% of the exposed subjects was greater than the current biological exposure index (BEI) for this substance, 35 µg/g of creatinine [23] (data not shown). As indicated, apart from age and length of employment, there were no statistically significant differences between the two groups as far as other variables were concerned. Mercury concentration in the ambient air was estimated to be $3.97 \pm 6.28 \mu g/m^3$, which did not exceed the current TLV for this substance, $25 \mu g/m^3$ [23]. However, in the past and before

TABLE 1. The Subjects' Demographic and Exposure Characteristics ($M \pm SD$)

Variables	Exposed (<i>n</i> = 46)	Nonexposed (<i>n</i> = 65)	p^{\dagger}
Age (years)	35.09 ± 9.90*	41.83 ± 5.91	.001
Height (cm)	171.43 ± 6.60	172.49 ± 6.76	.710
Weight (kg)	72.47 ± 9.89	72.51 ± 11.30	.260
Length of exposure/employment (years)	10.61 ± 10.90*	17.76 ± 5.82	.001
Atmospheric concentration of mercury (µg/m ³) [‡]	3.97 ± 6.28	—	_
Urinary mercury concentration (µg/dm ³)	34.3 ± 26.77*	10.15 ± 3.82	.001

Notes. †—independent *t* test, *—significantly different from their corresponding values for the referent group, $\ddagger -n = 12$.

TABLE 2. PI	revalence of	f Clinical S	Symptoms of	of Intoxication	in Exposed	(<i>n</i> = 46) and	Nonexposed
(n = 65) Sub	ojects (%)						

Symptoms/Signs	Exposed	Nonexposed	p [†]
Somatic fatigue	5 (7.7)*	15 (32.6)	.001
Mental fatigue	8 (12.3)*	15 (32.6)	.016
Loss of appetite	2 (2.1)*	8 (17.4)	.015
Writing difficulty	1 (1.5)*	6 (13)	.020
Loss of memory	7 (10.8)*	20 (43.5)	.001
Mood lability	10 (15.4)*	16 (34.8)	.023
Anxiety	21 (32.3)	18 (39.1)	.546
Agressive behavior	11 (16.9)	14 (30.4)	.110
Irritability	19 (29.2)	15 (32.6)	.835
Erethism	9 (13.8)	13 (28.3)	.090
Depression	6 (9.2)	10 (21.7)	.098
Insomnia	5 (7.7)	9 (19.6)	.083
Painful spasm of the extremities	5 (7.7)	7 (15.2)	.230
Gingivitis	5 (7.7)	7 (15.2)	.620
Irregular pulse	3 (4.6)	5 (10.9)	.272
Blurred vision	2 (3.1)	6 (13)	.064
Tremor	10 (15.4)	5 (10.9)	.581
Tachycardia	12 (18.5)	3 (6.5)	.093
Teeth problems	4 (16.2)	7 (15.2)	.195

Notes. $\dagger - \chi^2$ test, *-significantly different from their corresponding values for the referent group.

the authors' intervention, concentrations of mercury were remarkably higher than this value (up to $300 \text{ }\mu\text{g/m}^3$).

Table 2 displays the prevalence of different symptoms in both groups. As shown, symptoms such as somatic and mental fatigue, loss of appetite, writing difficulties and loss of memory were significantly more prevalent in the exposed group than in the referent one.

Multivariate logistic regression analysis revealed that symptoms such as somatic fatigue, loss of appetite, writing difficulty, loss of memory, mood lability, erethism, blurred vision and teeth problems were significantly more prevalent in exposed subjects even after adjusting for age, weight, height, years of employment and urinary mercury concentration (Table 3).

Laboratory results showed no significant differences between the two groups in red blood cells, white blood cells, blood urea nitrogen, levels or serum activity of liver enzymes. However, significant differences were noted between hemoglobin and hematocrit levels (Table 4).

TABLE 3. Association Between Exposure to Mercury and the Frequency (%) of Self-Reported Symptoms/Signs

Symptoms/Signs	β	Odds Ratio	p [†]
Somatic fatigue*	2.284	9.817	.001
Mental fatigue	0.051	1.052	.083
Loss of appetite*	1.892	6.632	.021
Writing difficulty*	2.847	17.233	.012
Loss of memory*	2.87	17.642	.001
Mood lability*	1.613	5.018	.003
Anxiety	0.298	1.347	.459
Aggressive behavior	0.764	2.148	.097
Irritability	0.158	1.171	.704
Erethism*	1.081	2.947	.034
Depression	1.005	2.731	.072
Insomnia	1.071	2.919	.072
Painful spasm of extremities	0.839	2.315	.193
Gingivitis	-0.441	0.643	.405
Irregular pulse	1.254	3.506	.119
Blurred vision*	2.471	11.837	.007
Tremor	-0.399	0.671	.495
Tachycardia	-1.177	0.308	.082
Teeth problems*	1.502	4.492	.033

Notes. †—multiple linear regression analysis, *—the prevalence of symptoms/signs marked with an asterix among exposed individuals was significantly higher than that of referent subjects.

Parameter	Exposed	Nonexposed	р
BUN (mg%)	17.07 ± 3.89	15.72 ± 3.62	.066
Bil total (mg/dm ³)	1 06 + 0 33	1 06 + 0 28	938

TABLE 4. Blood Parameters in Exposed (n = 46) and Nonexposed (n = 65) Subjects ($M \pm SD$)

Bil total (mg/dm ³)	1.06 ± 0.33	1.06 ± 0.28	.938	
ALP (U/dm ³)	213.82 ± 69.14	213.08 ± 65.57	.954	
AST (U/dm ³)	31.51 ± 9.44	30.68 ± 8.68	.634	
ALT (U/dm ³)	36.38 ± 23.46	32.02 ± 16.13	.250	
HB (g/dm ³)	14.97 ± 1.09	14.48 ± 1.10	.024	
HCT (%)	44.67 ± 2.40	42.82 ± 2.69	.001	
WBC (×10 ³ /mm ³)	5.88 ± 1.48	6.14 ± 1.36	.337	
RBC (×10 ⁶ /mm ³)	5.50 ± 0.32	5.44 ± 0.52	.456	

Notes. BUN—blood urea nitrogen, Bil—bilirubin, ALP—alkaline phosphatase, AST—aspartate amino transferase, ALT—alanine amino transferase, HB—hemoglobin, HCT—hematocrit, WBC—white blood cells, RBC—red blood cells.

Pearson correlation showed a significant association between urinary mercury concentrations and age (r = -.4, p = .04) as well as urinary mercury concentration and length of exposure (r = -.43, p = .03).

4. DISCUSSION

This study aimed to assess the health effects of occupational exposure of a group of employees of a local chlor-alkali plant to mercury. In this study, participants of both groups were from the same industry and had similar educational levels, gender, weight and height. Although the referent subjects were significantly older than the exposed group, abnormal symptoms were significantly more prevalent in the exposed subjects than in the unexposed group. Given the fact that none of the workers had personal or family history of neuropsychological disorders, these findings imply that the symptoms reported by the exposed subjects can be attributed to their occupational exposure to mercury.

Consistent with some other studies [13, 14, 17], prevalence of physical fatigue, mood and emotional changes and loss of memory in the exposed group were significantly higher than those of the referent group. In accord with our findings, Langworth, Almkvist, Söderman, et al. studied 89 workers exposed to mercury in a chlor-alkali unit with a history of 13.5 years of employment and mean urinary mercury concentration of 25.4 μ g/g of creatinine [13]. They reported that prevalence of symptoms such as mental disorders, fatigue, dizziness, sleep disorders, concentration and memory disorders was significantly higher in the exposed group than in the nonexposed one. In contrast, in some other studies, no significant differences were noted in the prevalence of neuropsychological disorders among the exposed group as compared with the referent one [7, 8].

Although the main reasons for these discrepancies are not clear, it seems that differences in the study design, and the level and length of exposure may explain, at least in part, these inconsistencies.

In this study, loss of appetite in the exposed group was significantly more prevalent than in

the referent one, which is similar to Langworth et al.'s result [13]. Furthermore, prevalence of writing difficulty in the exposed group was significantly higher than that of the referent one. Mathieson, Ellingsen and Kjuus reported similar findings [15]. Similarly, no significant difference was found between the heart rate of the two groups. These findings are in agreement with Piikivi [24].

No significant difference was found in the frequency of symptoms such as gingivitis, salivation or other oral problems in the exposed and the referent groups, although the frequency of these symptoms in the exposed group was higher than that of the referent one. These findings are consistent with Holland, Ellingsen, Olstad, et al.'s findings, in which no significant differences were observed between the groups in parameters such as the number of remaining teeth and oral health problems [25]. However, sudden loosening of teeth was observed in only 4 subjects with urinary mercury concentration over 1500 nmol/mmol of creatinine.

Frequency of symptoms such as painful spasm of the extremities, erethism and blurred vision in the exposed group was higher than in the referent group, although the differences were not significant when analyzed with univariate tests. However, multivariate logistic regression analysis revealed that these symptoms were more prevalent in exposed subjects even after adjusting for age, weight, height, years of employment and urinary mercury concentration. No significant differences were observed in the frequency of symptoms such as insomnia, irritability, aggressive behavior, anxiety or depression between the two groups, although the frequency of these symptoms in the exposed group was higher than in the referent one. Although these observations are in contrast with Langworth et al. [13], Piikivi and Hänninen [14] and Frumkin, Letz, Williams, et al. [17], it has to be noted that in Frumkin et al.'s study urinary mercury levels were lower than those in the present study (3.42 mg/dm^3) . Additionally, Frumkin et al.'s findings are questionable on biochemical and toxicological bases, as urinary mercury levels in the exposed workers with psychological symptoms were lower

than those of a nonexposed population, under $20 \ \mu g/dm^3 \ [26]$.

No significant difference was found between prevalence of hand tremor in the exposed and nonexposed groups. This finding is also in accord with the findings of other studies [7, 8, 10, 13, 14]. Similarly, in Piikivi and Hänninen's study, no significant differences were observed in the prevalence of hand tremor between the two groups [14]. However, a significant increase in the prevalence of hand tremor was found in exposed shift workers compared to office workers. Elingsen, Pettersen, Efskind, et al. also reported that no significant differences were detected between the prevalence of hand tremor in the exposed and referent groups, although a significant difference was found between the prevalence of hand tremor in smokers and nonsmokers [8]. Likewise, Wastensson, Lamoureux, Sällsten, et al. found no significant difference between prevalence of hand tremor in the two groups [11].

On the contrary, some studies reported increased prevalence of hand tremor in exposed workers [12, 17, 27]. This inconsistency may be caused by the different age and size of the studied population. Additionally, appearance of typical symptoms of mercury intoxication is likely when the level of urine mercury is equal to or greater than 100 μ g/dm³ [22]. Thus, it seems that urinary mercury concentration, age, length of employment and smoking may contribute to the presence of tremor.

Although mean values of hemoglobin and hematocrit in exposed individuals were significantly different from those in referent subjects, they were within normal range. Atmospheric mercury concentration measured in all parts of the plant was below the current value of TLV. This is due to daily washing of the plant with a concentrated solution of sodium thiosulphate and a proper use of the general ventilation system. These recommendations seemed to reduce atmospheric mercury concentrations from ~300 μ g/m³ in previous years to 3.9 μ g/m³.

Existence of a negative relationship between age and length of employment with urinary mercury concentration deserves comment. Although this finding apparently seems unusual, it should be noted that young workers with little job experience worked in the sections with the highest atmospheric concentrations of mercury. In contrast, older workers with more job experience worked in less polluted areas. This may explain this unusual finding.

This study has provided more evidence to confirm the hypothesis that neuropsychological symptoms can accompany occupational exposure to low levels of mercury. The BEI for this toxic metal has been set at 35 μ g/g of creatinine [23]. Since the normal value of urinary creatinine is 0.3–3 g/dm³ [22], the average amount of urine creatinine can be assumed to be 1.65 μ g/dm³. Thus, a simple calculation shows that the average acceptable level of urinary mercury in subjects occupationally exposed to this toxic metal is ~58 μ g/dm³.

In this study, the prevalence of neuropsychological symptoms in exposed workers with an average value of urinary mercury of $34.3 \pm 26.77 \ \mu g/dm^3$, below the current BEI, was significantly higher than that in referent subjects. While this finding may seem unusual, it should be emphasized that some studies reported significant increases in the prevalence of neurological symptoms in workers whose urinary mercury was lower than the BEI value [13, 14, 17].

Therefore, one might tentatively conclude that the current TLV and BEI values for this toxic metal do not provide sufficient protection against the occurrence of symptoms with toxicological importance, particularly neuropsychological ones. This proposition is in agreement with Richardson, Brecher, Scobie, et al., in that the relationship between mercury exposure and neurobehavioral outcomes in the development of a recommended exposure limit for mercury is generally neglected [28]. Additionally, these observations cast doubt on the appropriateness of the current value of BEI, per se, as a sensitive biological marker of exposure to mercury for early detection of intoxication. This conclusion is also indirectly implied by Ritchi, Gilmour, Macdonald, et al., who did not find any significant association between urinary mercury levels and the prevalence of toxicity symptoms [29].

Langworth et. al. [13], Piikivi and Hänninen [14] and Frumkin et al. [17] reported quantitatively similar findings to our study, in which a significant increase in the prevalence of symptoms among a group of chlor-alkali workers with urinary mercury concentration of 14.3 nmol/mmol of creatinine (25.4 µg/g of creatinine), 84.1 nmol/dm³ and 3.42 μ g/dm³ (2.76 μ g/g of creatinine), was observed. This notion is further supported by Holmes, James and Levy, who suggest that several potential symptoms of long-term environmental exposure to mercury are similar to those occurring from occupational exposure [30]. Finally, our findings are in line with the results of a recent study that demonstrated a decline in neurobehavioral performance of mercury-exposed subjects even at urinary mercury concentrations below 4 μ g/dm³ [31].

5. CONCLUSION

This study indicates that exposure to even low levels of mercury is likely to be associated with neuropsychological symptoms. Additionally, it provides circumstantial evidence to support the proposition that the current permissible levels of this toxicant do not provide sufficient protection against mercury-induced neuropsychological symptoms. Similarly, it causes uncertainty about the usefulness of the current value of BEI, per se, as a sensitive means for biomonitoring mercuryexposed subjects.

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