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Neuropsychological dysfunction related to earlier occupational exposure to mercury vapor

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Abstract

We assessed the neuropsychological test performances of 26 patients (mean age = 41.5 ± 6.1 years; mean years of education = 9.8 ± 1.8; 20 males) diagnosed with chronic occupational mercurialism who were former workers at a fluorescent lamp factory. They had been exposed to elemental mercury for an average of 10.2 ± 3.8 years and had been away from this work for 6 ± 4.7 years. Mean urinary mercury concentrations 1 year after cessation of work were 1.8 ± 0.9 µg/g creatinine. Twenty control subjects matched for age, gender, and education (18 males) were used for comparison. Neuropsychological assessment included attention, inhibitory control, verbal and visual memory, verbal fluency, manual dexterity, visual-spatial function, executive function, and semantic knowledge tests. The Beck Depression Inventory and the State and Trait Inventory were used to assess depression and anxiety symptoms, respectively. The raw score for the group exposed to mercury indicated slower information processing speed, inferior performance in psychomotor speed, verbal spontaneous recall memory, and manual dexterity of the dominant hand and non-dominant hand ($P < 0.05$). In addition, the patients showed increased depression and anxiety symptoms ($P < 0.001$). A statistically significant correlation (Pearson) was demonstrable between mean urinary mercury and anxiety trait ($r = 0.75$, $P = 0.03$). The neuropsychological performances of the former workers suggest that occupational exposure to elemental mercury has long-term effects on information processing and psychomotor function, with increased depression and anxiety also possibly reflecting the psychosocial context.

Key words
- Mercury, occupational exposure
- Cognitive assessment
- Neuropsychological dysfunction
- Neuropsychological tests

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Introduction

The nervous system is considered to be the main organ affected by elemental mercury vapor (1-4), with accumulation in the nervous cells appearing to persist throughout life (5). Nevertheless, mercury continues to be used for various industrial processes and products such as lamps, thermometers, barometers, etc.

Chronic occupational mercurialism is a condition defined by a set of symptoms developed after a period of inhalation of elemental (Hg^0) or inorganic mercury (Hg^{2+},

Hg^{3+}) vapor (6) during work, such as motor impairment, salivation, insomnia, memory losses, gingivitis (5), and erethism (7), which consists of changes of personality and behavior such as excitability and excessive shyness (8). It is a central nervous system syndrome (9) involving sensory losses that affect visual function (10-12), emotional disturbances (13) and personality changes including irritability, agitation, mood lability, shyness, and depression (5,8,14-16). Symptoms of mercurialism can be found in individuals with a history of chronic exposure to mercury vapor years after the exposure has ceased. In this case, urinary mercury levels will show normal values because urine excretion of large volumes of mercury occurs only during and shortly after exposure (5,7).

A number of studies have shown that cognitive dysfunctions develop in individuals exposed to mercury vapor. Some studies with industry workers currently exposed to mercury vapor have found deficits in short-term memory (17,18), mental arithmetic, switching attention, and reaction time (19), psychomotor function (19,20), logic memory, and manual dexterity (21). However, not all studies find changes in the same parameters (13,22,23) and this disagreement could not be explained by the exposure levels (23). Among the effects of mercury intoxication, motor impairment is apparently the most consistently reported symptom (9,23).

Neuropsychological evaluation was performed in most studies of intoxicated patients during the period of exposure to elemental mercury. Only a few have shown results of assessments after the cessation of the chronic exposure to mercury vapor (14,15,24-27). Some of these studies did not find significant differences between exposed and controls in any of the cognitive or motor functions assessed (25,27) while others have suggested that neuronal dysfunction is likely to be persistent even years after the end of chronic exposure (5,7,8,14,15,26). The likelihood of reversibility of the neuropsychological deficit is therefore controversial.

The purpose of the present study was to determine if there are long-term effects of exposure to elemental mercury vapor on cognitive and motor functions, as well as symptoms of depression and anxiety.

Material and Methods

Participants

Thirty-four former workers at a fluorescent lamp plant were recruited from the outpatient population (total mercury-intoxicated patients available = 44) of the Hospital das Clínicas (HC), Faculdade de Medicina, Universidade de São Paulo (FMUSP), São Paulo, SP, Brazil, where they had been treated. They had been exposed to elemental mercury vapor for 4 to 20 years (10.2 ± 3.8 years) and the period after cessation of exposure ranged from 1 to 18 years (6 ± 4.7 years). They were away from work because of health problems related to chronic occupational mercurialism and, in some cases, due to repetitive work. The inclusion criterion was a diagnosis of chronic occupational mercurialism and exclusion criteria were history of alcoholism, drug abuse, cerebrovascular or endocrine disease, head injury, or chelation treatment. The diagnosis of mercurialism was based on clinical examination, neurological evaluation, exposure history, and increased levels of mercury in urine during the time of exposure.

Control individuals (18 males and 2 females) were recruited and selected among the staff of the University of São Paulo where this study was conducted. A history of alcoholism, drug abuse, cerebrovascular, or endocrine disease, head injury, and acute or chronic exposure to mercury were the exclusion criteria. Thirty-two employees were recruited, 6 of whom were excluded because they were under 30 years of age (exposed participants ranged in age from 33 to 54 years), 2 reported endocrine disease, 1 had

an epileptic episode history, and 3 refused to participate. The demographic characteristics of the participants are summarized in Table 1.

No significant differences were found between the two groups regarding age or years of formal education.

Urinary mercury samples were analyzed by cold vapor atomic absorption spectrophotometry. Metal concentrations were determined using a calibration curve consisting of 5 standards. In order to ensure accurate measurements, the calibration curves were checked by the Levey-Jennings method (28) as a quality control procedure. The data on urinary elemental mercury levels (U-Hg; µg/g creatinine, Cr) were collected from the medical records of HC-USP. The urinary mercury levels during exposure were available for only 18 patients (46.8 ± 22.1 µg/g Cr). However, a high urinary mercury concentration could be estimated for the whole group because the former workers came from the same lamp production line.

Mercurialism can be found in individuals with normal U-Hg because the kidneys eliminate large volumes of mercury only during and shortly after the period of exposure (5,7). The mean U-Hg concentrations in the exposed group were normal 1 year after removal from exposure (1.8 ± 0.8 µg/g Cr). Thirteen patients were diagnosed with tendinitis (affecting one or both arms) related to repetitive work in manufacturing lamps. Twenty of them were taking medication for the treatment of depression and/or anxiety (Table 2).

Procedures

Each participant underwent neuropsychological assessment during a session of about 1.5 h of duration, which included a brief clinical interview and neuropsychological testing. The anamnesis included questions concerning the subjects' demographic data, job history, life-style habits, and clinical data. The patients were also asked about their occupational histories at the fluorescent lamp plant.

The neuropsychological battery included tests of attention, short term memory, and mental control (WMS Digit Span subtest) (29), inhibitory control (Stroop Interference

Table 1. Demographic characteristics of subjects exposed to mercury.

	Exposed group (N = 26)			Control group (N = 20)		
	N(%)	Mean ± SD	Median	N(%)	Mean ± SD	Median
Age (years)		41.5 ± 6.1	41.5		42.7 ± 8.2	42
Educational level (years)		9.8 ± 1.8	9.5		9.8 ± 2.2	11
Gender						
Male	20 (77%)	-	-	18 (90%)	-	-
Female	6 (23%)	-	-	2 (10%)	-	-
Work						
Employed	0 (0%)	-	-	20 (100%)	-	-
Away from work due to mercury intoxication	26 (100%)	-	-	0 (0%)	-	-
Alcohol consumption						
Drinkers	14 (54%)	-	-	15 (75%)	-	-
Non-drinkers	12 (46%)	-	-	5 (25%)	-	-
Smokers						
Current	2 (8%)	-	-	4 (20%)	-	-
Ex-smokers	2 (8%)	-	-	0 (0%)	-	-
Non-smokers	22 (84%)	-	-	16 (80%)	-	-

Data are reported as number of subjects with percent in parentheses, mean ± SD, and median. There were no statistical differences between groups in terms of age and education (independent *t*-test).

Table 2. Data related to the 26 mercury-exposed participants.

	N (%)	Mean ± SD	Range
Duration of exposure (years)	-	10.2 ± 3.8	4-33
Period since removal from exposure (years)	-	6 ± 4.7	1-18
U-Hg during the period of exposure (µg/g Cr)	18 (70%)	46.8 ± 22.1	20-73.8
U-Hg 1 year after cessation of exposure (µg/g Cr)	-	1.8 ± 0.9	0.8-2.8
Tendinitis diagnosis	13 (50%)	-	-
Psychoactive medication			
Antidepressants (tricyclics or serotonin reuptake inhibitors)	5 (19%)	-	-
Tranquilizers (benzodiazepines)	5 (19%)	-	-
Combined	6 (23%)	-	-
None	10 (39%)	-	-

Data are reported as number of subjects with percent in parentheses, mean ± SD, and range. U-Hg = urinary mercury levels; Cr = creatinine.

Test) (30), verbal memory (Buschke Selective Reminding Test, SRT) (30), visual memory (WMS Visual Reproduction subtest) (29), manual dexterity (Grooved Pegboard; Lafayette Instrument), verbal fluency (FAS) (30), visuomotor ability (WAIS-R Block Design subtest) (31), executive function (Wisconsin Card Sorting Test) (32), and verbal knowledge (WAIS-R Vocabulary subtest) (31). After this neuropsychological assessment the subjects were instructed to complete the Beck Depression Inventory (BDI) (33) and the State-Trait Anxiety Inventory (STAI) (34).

The study was approved by the Ethics Committee of the Psychology Institute, University of São Paulo, and all subjects gave written informed consent prior to testing.

Statistical analysis

Data with non-normal distribution (years of education, cognitive and motor tests, and mood inventory scores) were log-transformed to achieve normalization. Independent *t*-tests were applied to the continuous demographic variables (age and years of education) to assess differences between groups.

Group comparisons were made using the general linear model, which combines analysis of variance and regression procedures and allows the assessment of continuous and categorical variables (covariates/confounders) simultaneously. Dependent variables were the test scores. Assessment of potential confounding variables was taken into account. Age, raw score in the Vocabulary test as a measure of pre-morbid general ability, and drinking habits are potential confounders frequently considered in neuropsychological studies. BDI scores were also used as covariates because depression is reported to compromise cognitive functions (35,36). Since anxiety showed a high correlation with depression, STAI scores were not considered in order to avoid redundancies. Since antidepressants (tricyclic and serotonin reuptake inhibitors) and tranquilizers (benzodiazepines) can impair cognitive and/or psychomotor skills (37,38), the use (yes/no) of one or both medications was included in the analysis. A diagnosis of tendinitis (yes/no) was considered to be a potential confounder in the assessment of the tests that require manual motor performances (Visual Reproduction, Grooved Pegboard, and Block Design).

Pearson's correlation coefficients were calculated to detect possible associations between exposure to mercury variables (urine Hg^0 levels, duration of exposure and the time since the cessation of exposure) and neuropsychological performance within the exposed group.

Statistical analyses were performed using the MINITAB 14.0 software (39).

Results

The group exposed to mercury had significantly different scores compared to the control group on variables related to the SRT, Stroop Test, and Grooved Pegboard after accounting for potential confounders ($P < 0.05$). The medians and ranges of the score tests, F-ratios, and P values are reported in Table 3. The exposed participants a) took a longer mean time in naming colors in the Stroop Test parts 1 ($P = 0.03$) and 2 ($P = 0.01$), but not in part 3 ($P = 0.09$), b) showed lower scores for verbal memory on the SRT long-term recall ($P = 0.03$), long-term storage ($P = 0.00$), consistent long-term recall ($P = 0.01$), and delayed recall ($P = 0.00$), c) showed longer mean times in manual dexterity with the dominant hand ($P = 0.00$) and the non-dominant hand ($P = 0.00$) in the Grooved Pegboard test. Exposed participants also had higher scores in the depression (BDI) and anxiety (STAI) inventories ($P = 0.00$; Figure 1).

A salient feature was the profile of the exposed group within the tests. Compared

with the control group, the former workers showed poorer results in the Stroop Test parts 1 and 2, that mainly require information processing and psychomotor speed, but not in part 3, a measure of inhibitory control. Indeed, their low SRT scores in long-term recall and consistent long-term recall suggest impairment of primary verbal memory spontaneous recall. In contrast, the cued recall scores were not statistically different between groups, indicating the integrity of verbal memory storage ability in the exposed group, but a difficulty in spontaneously recalling the stored words. Although the groups differed significantly in long-term storage, this sub-item only reflects the sum of words recalled in two consecutive trials without being reminded during testing.

The associations between the exposure indicators and the patient's neuropsychological performances calculated by Pearson correlation coefficients are presented in Table 4. The urinary mercury concentration measured 1 year after the end of exposure was significantly correlated only with the STAI score ($r = 0.75$; $P = 0.03$). The concentrations of mercury in urine at the time of exposure, duration of exposure and the period of removal from exposure were not correlated with any test or inventory score (Table 4).

Discussion

The present study focused on determining if neuropsychological and motor impairment could be detected in a group of workers formerly employed by a fluorescent lamp plant. They had been away from the source of exposure for an average of 6 years (1 to 18 years) and had a diagnosis of chronic occupational mercurialism.

The exposed subjects showed reduced performance in specific neuropsychological functions and motor skills. There were slowed information processing speeds (Stroop test parts 1 and 2) and impairment in verbal memory (SRT), hand-eye coordination, and manual dexterity (Grooved Pegboard). We also found symptoms of depression (BDI) and anxiety (STAI) in these patients. When analyzing the verbal memory performance of the exposed subjects it is important to emphasize that although they failed long-

Table 3. Comparison of test scores between subjects exposed to mercury and controls.

Tests	Exposed group		Control group	
	Median	Range	Median	Range
Digit span				
Forward	5	1-9	6	3-9
Backward	4	0-9	4	2-6
Stroop (time in s)				
Part 1	17*	13-55	14	9-27
Part 2	22.5*	14-82	17	11-42
Part 3	32.5	19-69	29	16-56
SRT				
Total number of words	88	40-124	107	44-126
Long-term recall	63*	5-119	89.5	22-122
Long-term storage	86*	9-125	103	6-130
Consistent long-term recall	34*	0-96	64	10-130
Random long-term recall	30	5-57	25.5	9-60
Delayed recall	8*	2-12	9	6-12
Cued recall	11	4-12	12	9-12
Intrusions	2	0-14	0.5	0-8
Visual reproduction				
Immediate recall	24	6-40	26	8-34
Delayed recall	17.5	1-39	22.5	2-31
FAS				
F	10	1-19	11	6-18
A	7.5	2-18	11	7-16
S	7	1-16	9	3-15
Total	25	2-50	32.5	20-49
Grooved pegboard (time in s)				
Dominant hand	79*	69-130	75.5	46-99
Non-dominant hand	95*	76-177	82.5	60-120
Block design	20	3-38	22	3-43
Wisconsin				
Errors	66	14-97	52.5	11-97
Perseverative errors	36	8-96	23	5-94
Completed categories	2	0-6	4	0-6
Vocabulary	28	20-39	33	10-53

Data are reported as median and range. SRT = Buschke Selective Reminding Test; FAS = verbal fluency.
*$P < 0.05$ compared to controls (general linear model analysis).

term and delayed recall, they performed in the normal range in cued recall, suggesting a deficit in spontaneous recall. Our hypothesis is that the poor results of verbal learning ability are related to information processing deficit. High BDI and STAI scores were expected, since depression and anxiety are symptoms of chronic mercurialism. Nevertheless, the possibility that these symptoms are associated with psychosocial problems related to being unemployed could not be ruled out. In this case, depression and anxiety would represent a reaction to the psychosocial context.

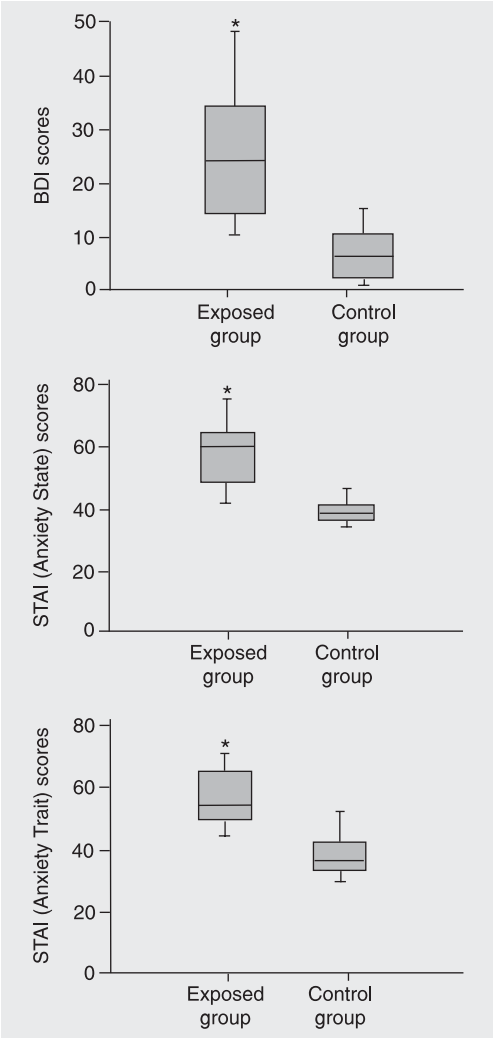

Figure 1. Box plots representing the performances (median, first and third quartiles, and 95 and 95 percentiles) of exposed and control participants on the Beck Depression Inventory (BDI) and State-Trait Anxiety Inventory (STAI) (P = 0.00). U-Hg = urinary mercury levels. P < 0.05 compared to control (independent *t*-test).

Table 4. Pearson correlation coefficients between exposure variables and tests and inventory scores among former workers.

Variable	Domain	r	P
Duration of exposure	All tests and inventories	-	
Period since removal from exposure	All tests and inventories	-	
U-Hg during the period of exposure	All tests and inventories	-	
U-Hg 1 year after removal of exposure	Anxiety trait (STAI)	0.75	0.03
	Other tests and inventories	-	

U-Hg = urinary mercury levels. See Procedures in Material and Methods. -, no correlation.

Few investigations have focused on the question of cognitive impairment association with past exposure to mercury vapor (14,15,24-27). Our findings in terms of preserved functions were consistent with previous studies that failed to detect impairment of immediate memory (24-27), vocabulary (24-26), and viso-spatial ability (14,15,24).

Our results agree with the slowed information processing speed (test of color card reading) and motor deficits found in ex-miners (U-Hg = 3.2 ± 4.1 ng/g) who were previously exposed to high levels of mercury vapor for 15.5 years on average (SD = 8.7) (14,15). However, we did not detect visuo-spatial or short-term memory deficits. A possible explanation is the fact that the previous study examined ex-miners of a mercury mine 18 years after the end of exposure and certainly included individuals who were older and had been exposed to higher mercury vapor concentrations than in the present study. Indeed, a correlation was observed between the number of years after the cessation of exposure and better performance in the short-memory test (Digit Span) (15).

Mathiesen et al. (24) also found motor, psychomotor, visuomotor, and attention deficits in former workers of a chloralkali plant (mean U-Hg = 1.8 ± 1.3 nmol/mmol Cr) who had been exposed to mercury vapor for 7.9 ± 6.8 years (time since the end of exposure = 12.7 ± 11.7 years). In contrast to our results, scores in a visual memory ability test were also decreased, particularly in individuals with high cumulative exposure levels (U-Hg ≥3000 nmol/L). On the other hand, Bast-

Pettersen et al. (27) did not find visual memory impairment in former chloralkali workers (mean U-Hg = 1.65 nmol/mmol Cr, range 0.2-5.2 nmol/mmol Cr) exposed to mercury for 13.1 years on average (range 2.8-34.5) and removed from exposure for 4.8 years (range 4.2-10.0). The majority of these participants had been examined during the period of exposure in a previous study (22) that reported impairment of immediate visual memory, suggesting recovery of function.

Our findings of verbal memory impairment support previous studies that showed a significantly worse performance in a list learning test (26) and in a word pair test (individuals with the highest intensity of exposure showed a deficit) (24) in former employees of a chloralkali plant. In contrast, Letz et al. (25) did not detect statistical differences in verbal memory between former workers of a heavy industrial plant and controls. However, these discordant findings may reflect the time since the cessation of exposure (30 years or more).

Motor dysfunction associated with a history of past exposure to mercury vapor has been well described. In the present study, there was a significant difference between exposed participants and controls in the Grooved Pegboard test that required manual dexterity and hand-eye coordination. Indeed, the general linear model analysis was done considering a diagnosis of tendinitis to be a confounder, and this variable was not significantly associated with motor performance. Previous studies conducted after the cessation of exposure to mercury detected impairment of motor coordination (14,15), manual dexterity (14,15,24,26), and reaction time (14,15,24). Letz et al. (25) reported a significant association between hand-eye coordination and cumulative mercury exposure in former workers examined 30 years after the end of exposure.

The present study found no association between the impairment detected in the patients and duration of exposure to mercury or length of the period away from exposure. Because of the variability among the workers' job categories in the plant, the degree of exposure was also variable, and therefore the failure to detect significant relationships is not surprising. Similarly, urinary mercury levels during the time of exposure were not observed to be associated with any test or inventory score. It is possible that effects of U-Hg on cognitive and motor functions were not detected because of the small sample size. However, urinary mercury concentration measured 1 year after the end of exposure correlated positively with the anxiety trait (STAI). Mercury intoxication has been reported to provoke changes in personality traits as a symptom of erethism (3,13). Alterations have been reported even at very low exposure concentrations, such as higher trait anxiety scores in women exposed to elemental mercury from dental amalgams compared to women with no dental fillings, attributed to a possible dysfunctional norepinephrine metabolism (40).

The limitations of the present investigation are mainly related to the demographic characteristics of the groups studied. A larger sample size might have helped detect other possible cognitive dysfunctions related to mercury exposure. Another problem is the variable duration of exposure and time after the end of exposure. Indeed, there were changes in type of occupation during employment, with different mercury vapor levels in the air in different occupations.

Former workers of a fluorescent lamp plant manifested slowed information processing and impaired psychomotor performance many years after cessation of exposure, showing that there might be persistent damage in neurobehavioral functions due to long-term exposure to mercury. The mood disturbances observed are expected in individuals with chronic occupational mercurialism but may also reflect psychosocial problems. Further longitudinal work on this sam-

ple is recommended to confirm whether or not the neuropsychological and motor deficits observed persist for many years.

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