Chronic Mercury Exposure Examined With a Computer-Based Tremor System

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Tremor is being increasingly evaluated by quantitative computer-based systems to differentiate its causes. In this study, a group of mercury-exposed workers were assessed to determine whether tremor characteristics differed by exposure level. Workers were classified into two groups: those with an average urine mercury concentration below the American Conference of Government Industrial Hygienist Biological Exposure Index of 35 μg/g creatinine, and those with an average urine mercury concentration above the Biological Exposure Index. Tremor characteristics (including intensity, harmonic index, center frequency, standard deviation of the center frequency, and tremor index) were measured and recorded with a computer-based tremor system. Sixteen of 17 workers who were potentially exposed to mercury participated in the study. Three workers had a mean urine mercury concentration of 27.0 μg/g-creatinine and were assigned to the low-exposure group, and 13 workers had a mean urine mercury concentration of 200.2 μg/g-creatinine and were assigned to the high-exposure group. There was a statistically significant difference in the tremor index (which compiles five individual tremor parameters into a single value) between the two groups (P = 0.04; Wilcoxon's rank sum test). Other tremor characteristics did not differ significantly between the groups. Tremor index may be more useful than measures of individual tremor parameters in differentiating normal from subclinical pathological tremors among groups of workers with chronic mercury exposure. (J Occup Environ Med. *2001;43:295–300*)

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Tremor is an involuntary rhythmic oscillation of any body part and can represent either a physiological process or a manifestation of disease.[1] The oscillatory movements are produced when alternating or synchronous agonist-antagonist muscles contract rhythmically. Because of the rhythmicity, tremors lend themselves well to accurate transduction and quantification. The amplitude and the frequency of the oscillation can vary, as can the factors that precipitate the movement. Traditionally, amplitude and frequency have been used to classify the etiology of the tremor and to differentiate normal from pathological tremors.[2] Unfortunately, diagnostic misclassification is common because these tremor characteristics lack the desired specificity.

Despite the general lack of specificity, researchers have tried to determine which tremor characteristics are associated with exposure to mercury, a heavy metal known to cause tremors.[3] Characterizing tremor patterns associated with mercury toxicity may be potentially useful as an indicator of nervous system integrity; however, the results of previous investigations are inconclusive.[4–9] Some studies have found that tremor frequency increased with mercury exposure,[9] decreased,[10] or remained stable.[11] Tremor amplitude has been generally reported to increase with mercury overexposure, but the increases have not consistently been statistically significant.[12] The inconsistencies of tremor characteristics also seem to be due to the different methods used to evaluate tremors and to the complex and fluctuating nature of tremors.[13]

Given the inconsistencies of frequency and amplitude in characterizing tremors associated with mercury overexposure, other measures, such as tremor indexes (which compile individual tremor parameters into a single value), may more accurately assess subtle tremor changes.[14] The aim of this study was to assess whether the TREMOR 3.0™,[15] a lightweight accelerometer that quantitates individual tremor parameters and indexes, can be used to differentiate between the tremor characteristics of workers who have longstanding elevated urine mercury levels and those with low levels. Also, we report the quality indicator, a summary description of the tremor parameters reported as three discrete values, which has not been previously reported as it relates to mercury exposure.

Methods

Sixteen of 17 workers at a mercury recycling plant participated in the investigation. The workers were not exposed to other neurotoxins at work, and none of the workers had a personal or family history of essential tremor or a personal history of any neurological condition that may cause tremor. The investigation included a self-administered questionnaire (which included questions about demographics; work history; work practices; personal and family medical history; non-occupational sources of mercury exposure; personal habits and hobbies; and symptoms associated with mercury overexposure, such as nervousness, irritability, emotional lability, depression, weakness, tremor, insomnia, gingivitis, numbness, respiratory symptoms, rash, increased salivation, headache, and metallic taste in the mouth); a complete neurological examination by a neurologist; a neurometer test (which tests sensory nerve function); color vision tests; a grooved pegboard test (which tests fine psychomotor control); and a tremor test.[16] The questionnaire results revealed that six workers reported symptoms of mercury overexposure. Nine workers showed evidence of a mild upper-extremity tremor on neurological examination but no overt signs of mercury toxicity. Also, there was no association between having a tremor on examination and urinary mercury concentration. The results of the neurometer, color vision, and grooved pegboard tests showed no association with mercury concentration. The results of the tremor test are the focus of this report.

Tremor Test

Tremor characteristics of the upper extremities were measured using the TREMOR 3.0 developed by Danish Product Development.[15] This device measured tremor characteristics with a two-axis micro-accelerometer embedded in the tip of the 12 × 0.8-cm pencil-shaped instrument, called the TREMOR PEN™. The micro-accelerometer was sensitive in a plane perpendicular to the tube axis. During a 10-second test (2 seconds for stabilization and 8 seconds for data harvest), the TREMOR PEN was held like an ordinary pencil. Hand vibrations were recorded and displayed in real time in a time-axis plot on a computer screen. Measurements derived from acceleration are based on the Fourier power spectrum, which gives a power distribution of the data in the frequency domain. It is composed of 116 discrete values in the 0.9- to 15-Hertz (Hz) range, each approximately 0.12 Hz apart. The Fourier power spectrum is reported to react strongly to deviant tremor patterns, which have a tendency to concentrate power dissipation around a dominant frequency.[17]

The tremor test was performed with participants sitting erect with their back away from the backrest. Participants held the pen horizontally at navel level with the elbow bent approximately 90 degrees. Testing was done with both dominant and non-dominant hands to yield test 1. The procedure was then repeated, yielding test 2. Normal performance on the TREMOR 3.0, as defined by the manufacturer, was derived at the Clinic of Occupational Health, Copenhagen, Denmark.

The tremor parameters measured by TREMOR 3.0 include the tremor intensity (I), center frequency (F50), standard deviation of center frequency (SF50), harmonic index (HI), and tremor index (TI). Each parameter is described as follows:

- I is the root-mean-square of accelerations recorded in the 0.9- to 15.0-Hz band during the 8-second test period. This parameter represents the amplitude (maximum displacement) of the tremor.
- F50 is the median frequency of accelerations in the 0.9- to 15-Hz band during the 8-second test period. Fifty percent of the energy that drives the tremor is produced at frequencies above the center frequency, and 50% is produced below the center frequency.
- SF50 indicates the degree of irregularity of the tremor. Sixty-eight percent of the area of the spectrum lies within ±1 standard deviation of the center frequency. A very rhythmic tremor has a small SF50, indicating that most of the energy is produced within a narrow frequency band.
- HI compares the tremor frequency pattern with a pattern of a single oscillation, which has an HI of 1.00. A tremor composed of few dominating frequencies will have a high HI, whereas the normal disorganized tremor will have a relatively low HI.
- TI is a single measure incorporating the five measures of I, F50, SF50, HI, and the standard deviation of the harmonic index (SHI). One advantage of the TI is that any value deviating significantly from the norm will contribute a relatively smaller amount to the TI. The normal value for TI is 100, and the normal dispersion is ±20. In general, a TI below normal indicates poorer function, but this

interpretation is equivocal. The manufacturer gives no specific clinical meaning to TI results. The TI can be calculated from the following formula:

$$TI = F \sum_i (a_i \exp(-|(K_i - M_i) \div S_i|),$$

where F is a scaling factor that adjusts to make the mean of the test sample of normal subjects equal to 100. The value of a_i is 1/6 for all tremor parameters except I, for which a_i is 1/3. K_i represents the measured values of the tremor parameters from which the TI is calculated (I, F50, SF50, HI, SHI). M_i represents the normal human mean for the tremor parameters, and S_i represents the SD for the parameters.

- Quality indicator, scored as A, B, or C, reports how many of the five measured parameters from which the TI is calculated are within the normal dispersion range. (Each test was repeated to make 10 test results per participant.) With an A score, 9 to 10 parameters are within the mean ± 1 SD; with a B score, 4 to 8 parameters are within the mean ± 1 SD; and with a C score, three or fewer parameters are within the mean ± 1 SD.

Urine Mercury Concentrations

Beginning in July 1998, all workers in the plant had spot urine mercury concentrations measured. The initial results revealed elevated levels in most workers. Those with elevated urine mercury concentrations had the test repeated monthly. Those who did not have elevated levels had the test repeated in August and November. Mean urine mercury concentrations were calculated for each employee from surveillance results that were collected from July 1998 through November 1998. The tremor test was administered in September 1998.

The cold vapor atomic absorption method was used to determine the urinary mercury concentrations. The limit of detection for this method is 0.3 to 0.4 μg/L. The precision was 3.1% to 4.9% relative SD at concentrations of 30 μg/L. The trueness, based on recovery studies, was 99%.

Statistical Analysis

Participants were placed in one of two separate groups. Those with a mean urine mercury concentration below the American Conference of Government Industrial Hygienists Biological Exposure Index of 35 μg/g of creatinine were assigned to the low-exposure group. Participants with an average concentration above the Biological Exposure Index were assigned to the high-exposure group. Because the number of participants was small, only two exposure groups were used for calculations. In addition to using the Index as the cutoff for dichotomizing the data, urinary mercury concentrations of 50 to 300 were used as cutoffs; as the cutoff value increased, the tremor parameters became less distinct between the groups.

Because of the small sample size and non-normality of the data, nonparametric analytic methods were used. For continuous variables, the significance of the difference between the two groups was obtained by the Wilcoxon's rank sum test. The significance of the difference for dichotomous variables was obtained by Fisher's exact test. Kruskal-Wallis one-way analysis of variance was used to test the significance of the difference between the Quality Indicator scores and urinary mercury concentration. Also, Spearman's correlation coefficients were calculated, but there was little correlation between the tremor parameters and urinary mercury concentrations.

Results

Three participants were assigned to the low-exposure group and 13 to the high-exposure group. The two groups were similar in their demographic characteristics and personal habits, except that the low-exposure group had a higher proportion of current cigarette smokers and less tenure at the plant (Table 1).

A comparison of the tremor parameters between the low-exposure and the high-exposure groups was made. There were slight differences between the two groups for tremor intensity, harmonic index, center frequency, or standard deviation of center frequency. However, the tremor index showed a statistically significant difference between the two groups; the tremor index of the high-exposure group was 27% lower than that the low-exposure group (a lower tremor index indicates poorer performance [Table 2]). Although the difference in the tremor index was statistically significant, there was substantial overlap (Fig. 1). All three workers in the low-exposure group were within the range of normal values for the tremor index (above 80), but 5 of the 13 workers in the high-exposure group had tremor indexes above 80 as well.

A poorer quality indicator score was found with increasing urinary mercury concentration (more tremor parameters are within normal limits with A than B, and more parameters are with normal limits with B than C), but the difference among the scores was not significant (Table 3). There was considerable spread of the urine mercury concentrations within the quality indicator score. Participants in the high- and low-exposure categories had both A and B quality indicator scores, but only participants in the high-exposure group received C scores (three or fewer of the tremor parameters within normal limits).

Discussion

Early studies reported that pronounced tremors occurred with mercury exposures associated with urinary mercury concentrations of 300 μg/g creatinine,[18] but more recent studies have reported tremors associated with occupational exposures that produced urinary concentrations of 50 to 100 μg/g creatinine and blood levels of 10 to 20 μg/L.[19] In our study, we found that most of the tremor characteristics did not differ

TABLE 1
Urine Mercury Concentration and Demographic Observations in High-Exposure and Low-Exposure Groups

	Exposure Category*				
	<BEI (*n* = 3)		≥BEI (*n* = 13)		
Categories	*n*	Range	*n*	Range	P Value
Age (yrs)	29.7	18.0–46.0	33.1	23.0–47.0	0.46†
Men (%)	100.0		76.9		0.89‡
White (%)	100.0		92.3		0.91‡
Caffeine use§	2.0	1.0–4.0	3.2	0.0–12.0	0.58†
Alcohol use‖ (%)	100.0		76.9		0.89‡
Current smokers (%)	66.7		15.4		0.10‡
Education level¶	2.7	1.0–5.0	2.1	1.0–5.0	0.56†
Workplace tenure (months)	1.2	0.2–3.0	12.2	3.0–38.0	0.02†
Average urinary mercury level (μg/g creatinine)	27.0	24.9–31.2	200.2	52.9–939.7	0.01†

* BEI, American Conference of Government Industrial Hygienist's Biological Exposure Index. The BEI for mercury is 35 μg/g creatinine.
† *P* value calculated by Wilcoxon's rank sum test.
‡ *P* value calculated by Fisher's exact test.
§ Number of caffeinated beverages consumed daily.
‖ Drank more than 20 alcoholic beverages in lifetime.
¶ Highest level of education attained; 1, grades 1 through 12; 2, some college; 3, college graduate; 4, graduate degree.

TABLE 2
Mean (±SD) Tremor Test Parameter* by Mercury Exposure Group

Tremor Test Parameter	<BEI† (*n* = 3)	≥BEI (*n* = 13)	*P* Value‡
Tremor index	115.0 ± 12.2	83.6 ± 23.2	0.04
Tremor intensity (m/s^2)	0.13 ± 0.02	0.16 ± 0.05	0.38
Harmonic index	0.90 ± 0.01	0.88 ± 0.04	0.44
Center frequency (Hz)	6.80 ± 1.46	7.16 ± 1.73	0.80
Standard deviation of center frequency (Hz)	3.52 ± 0.48	3.35 ± 4.73	0.59

* See Methods for definitions of tremor test parameters.
† BEI, Biological Exposure Index. The BEI for mercury is 35 μg/g-creatinine.
‡ *P* values were calculated by the Wilcoxon's rank sum test.

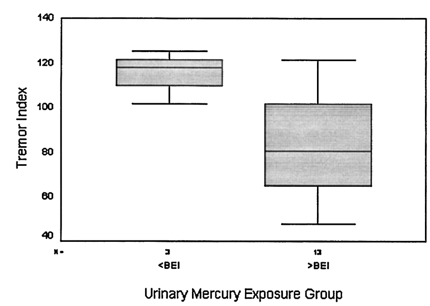

Fig. 1. Tremor index by Biological Exposure Index group. The tremor index is a parameter calculated from the five other tremor parameters (center frequency, harmonic index, tremor intensity, standard deviation of center frequency, and standard deviation of the harmonic index). The box plot shows the median, interquartile range (shaded area), and extreme values for each group.

between workers with urinary concentrations below 35 μg/g creatinine compared with those having the higher concentrations. However, the most striking difference was a lower tremor index in the high-exposure group. Higher-quality indicator scores seemed to correspond to higher urine mercury concentrations, but there was overlap between A and B scores in both exposure groups. Only workers in the high-exposure category had C scores (three or fewer of the measured tremor parameters were within the mean ± 1 SD of the normal values). Thus, these results show that the indexes, namely, the tremor index and quality indicator scores, corresponded better to urine mercury concentrations than the individual tremor parameters among this group of workers.

Two previous studies used the TREMOR 3.0 to compare tremor characteristics after exposure to inorganic mercury. Netterstrom et al analyzed the tremor characteristics of both a "low-exposure" group (acute exposure to elemental mercury) and a control group and repeated this analysis 3 and 16 months later.[9] Their results showed that tremor intensity was higher in their low-exposure group (although this difference was not statistically significant); other tremor characteristics were smaller and did not approach significance. Biernat et al studied mercury-exposed gold traders and found that tremor intensities in the 6.6- to 10-Hz range of the gold traders were significantly higher than the tremor intensities of the controls.[20] Tremor indexes and quality indicators were not mentioned. Our study showed a slight increase in tremor intensity in the high-exposure group, but this result was not statistically significant.

Our study has several limitations. Because of the size of the study population, more robust parametric statistical tests could not be used to

TABLE 3
Average Urinary Hg Level by Quality Indicator Score*

Quality Indicator Score	Mean Urinary Hg Level (μg/g Cr)	P Value†
A	80.8 (76.3)‡	0.13
B	148.9 (222.1)	
C	234.5 (260.8)	

* Hg, mercury; Cr, creatinine. Quality indicator, scored from A to C, reports how many of the measured parameters from which the tremor index is calculated, are inside the dispersion range of the human normal group. With an A score, 9 to 10 parameters are within the mean ± SD; with a B score, 4 to 8 are within the mean ± SD; and with a C score, 3 or fewer parameters are within the mean ± SD.

† *P* value calculated by Kruskal-Wallis one-way analysis of variance. The *P* value was not adjusted for multiple comparisons.

‡ Values in parentheses indicate SD.

evaluate the difference between groups. In addition, the small number of participants in the low-exposure group made the statistical calculations less stable. Another limitation is that all participants had some degree of exposure to mercury, so there was no unexposed group. Also, tremor patterns can vary over time, so single assessments of individuals may be misleading. Our measurement of tremor characteristics occurred several months after the initial exposures, and the mercury levels were decreasing at the time of testing. Several studies have shown that tremor characteristics improve with decreasing urine mercury concentrations,[9,21–23] so the tremor characteristics may have improved in the high-exposure group, which would decrease the differences in tremor characteristics between groups.

The question of how best to characterize and quantify aspects of tremor effectively is of interest to clinicians and researchers, especially because portable computer-based systems for tremor evaluation using spectral methods are now commercially available. However, the accurate measurement of tremor is only the first step in the utility of such a system as a clinical tool; valid interpretation of the results is also necessary. The difficulty with preclinical detection of neuromotor dysfunction, such as pathological tremors, is that the manifestations are usually subtle, often intermittent, and similar for different causes.[24] This problem is more pronounced when searching for subclinical (low-amplitude) signs of pathology in tremor (normal subjects may have clinically detectable tremors, ie, physiological and enhanced physiological tremors),[25] but computerized systems may be the most useful in these situations.[14]

An index from a computer-based system may be of most use for clinical purposes, but research continues to define the most appropriate index to differentiate normal from pathological tremors. The tremor index from the TREMOR 3.0 is relatively insensitive to only one abnormal characteristic and requires several characteristics to be abnormal before it is outside the reference range. This conservative approach prevents some abnormal tremors from having values outside the reference range of the tremor index.[14]

Tremor amplitude and frequency often do not clearly differentiate subjects with long-standing elevated mercury levels. However, tremor index may be a better marker of the subtle changes that can occur with mercury toxicity by group. Our findings confirm the principle that tremor characteristics may differ among some workers with high mercury exposures, but the tremor characteristics are not consistently abnormal in those with elevated mercury levels. This principle is consistent with other studies showing that mercury concentrations in body fluids have commonly failed to relate well to neurological outcome measures on an individual basis.[9] Because of the inconsistency of these and other findings, further research is needed to determine which tremor characteristics are most predictive of subclinical neurotoxicity. Also, serial measurements of tremor characteristics would be of value to demonstrate change in tremor patterns.

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Harper's Index

Hours during which free speech is permitted in Singapore's Hong Lim Park: 7 AM to 7 PM.

Percentage of US budget devoted to foreign developmental aid in 1962 and 2000, respectively: 3 and 0.5.

Average annual number of male clients served in America in 1999 by each female prostitute: 694.

Rank of repetitive motion among factors that correlate with forearm pain among workers: 2.

Amount Florida state employees donated to the 2000 Bush campaign for every dollar donated to Gore: $4.92.

Average age of new US grandparent in 1999: 47.

Year in which the levered voting machines used in some precincts last November were invented: 1892.

Change since 1981 in minutes per day devoted to homework by American children between 9 and 11 years old: +9 minutes.

—HARPER'S INDEX. *Harper's Magazine.* 2001;302(1808):13.