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NEUROLOGIC EFFECTS OF INCREASED LEAD ABSORPTION. A LONGITUDINAL STUDY

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ABSTRACT

This report summarizes the first phase of a longitudinal study designed to identify subclinical neurologic alterations in apparently healthy workers from a secondary lead smelter. Examination included multiple biochemical indices of increased lead absorption, a neurologic symptom questionnaire, standard neurologic examination; nerve conduction measurements, quantitative oculomotor function tests and detailed auditory testing. Lead workers and controls were intermixed so that the examiners were unaware of the status of any individual being tested.

The lead workers had significantly more neurologic symptoms than the controls but relatively few differences were found on the quantitative neurologic testing. We were unable to confirm previous reports of nerve conduction slowing in lead workers with consistently low blood lead levels. The accuracy of saccadic eye movements was significantly different in the lead workers and controls but saccade accuracy was not significantly correlated with blood lead concentration in the lead workers. Saccade delay time was highly correlated with blood lead concentration in the lead workers ($r = 0.412$, $p < 0.001$). The scatter in delay time measurements in both controls and lead workers, however, would preclude its use as a reliable indicator of increased lead absorption in a single lead worker. Repeat testing in the same subjects should help clarify the significance of these baseline findings.

Occupational exposure is the main source of increased lead absorption in adults and although improved medical surveyance has decreased the number of overt cases of lead poisoning, the consequences of long-term increased lead absorption in asymptomatic workers is still a major concern. An upper limit of 80 μg/100 ml of lead in blood has been set in the United States as the upper limit

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of safe occupational lead absorption but many investigators are concerned that this does not, in fact, provide adequate protection. There are reported examples of neurologic impairment in workers with blood lead levels consistently below 80 μg/100 ml[12,15,11]. The reversibility of these abnormalities and whether they lead to overt symptoms and signs of poisoning is not yet determined.

Our study was designed to identify subclinical neurologic alterations in apparently healthy lead workers with blood lead levels below 80 μg/100 ml and to study the progression or reversal of any such alterations with time. The study is being carried out over a three-year period in three phases: 1) a baseline examination including a questionnaire outlining the medical history, standard neurological examination, biochemical measurements for lead, arsenic and cadmium absorption, quantitative ocular motor function tests, nerve conduction measurements and standard auditory testing; 2) a follow-up period with monitoring of biochemical indices and 3) repeat of all baseline testing. This report summarizes the results of the baseline testing in the lead workers and controls.

METHODS

Subject selection

The study group consisted of 69 workers from a secondary lead smelter in Southern California. Because of the high turnover rate of workers in this industry, only employees with at least one year of employment were eligible for inclusion in the study. Longitudinal blood lead measurements (for at least one year) from the company's medical surveillance program were available on 136 potential study group workers. Workers were selected from this list to represent a range of blood lead values with the majority between 60–80 μg/100 ml.

The control group consisted of 35 workers from three nearby aluminum processing plants chosen because of similarity to the study group plant in workforce characteristics, noise exposure, type of industrial operations and physical activity of the employees, and for lead, arsenic and cadmium exposure comparable to those in the general community. Only those workers who had at least one year with the company were selected for the control group.

Demographic characteristics of the lead workers and controls and background environmental data from their workplaces are reported in detail elsewhere[17]. In brief, the groups were comparable for age, race, smoking, alcohol use and education. The lead group differed from the control group in exposure to arsenic as well as lead since the smelter recovered lead mostly from old automobile batteries. The noise exposure in the four plants was similar.

Biochemical studies

Blood was collected from each participant at the time of neurologic testing. Whole blood lead concentration was determined by atomic absorption spectrophotometry[6], red blood cell δ-aminolevulinic acid (ALA) by the method of Burch and Siegel[5], and free erythrocyte protoporphyrin (FEP) by the method

of Piomelli[10]. Hair, red blood cell and plasma lead, arsenic and cadmium levels were determined by a modified Delves technique for atomic absorption spectrophotometry[4].

Neurologic examination

The examination was performed by an experienced neurologist with particular attention directed toward identifying early signs of peripheral neuropathy. The results of the examination were recorded on a standardized form insuring completeness and consistency.

Oculomotor function tests

The electro-oculography (EOG) test battery included tests of saccades, smooth pursuit and optokinetic nystagmus. Saccadic eye movements were induced by having the subject follow a target moving stepwise with random amplitude and intervals between jumps[3]. The maximum velocity-amplitude relationship, delay time and accuracy of recorded saccades were determined by a laboratory digital computer[1]. Smooth pursuit was induced by a target moving sinusoidally at 0.2 and 0.4 Hz (maximum excursion 36 degrees). The gain of the pursuit system (eye velocity/target velocity) was calculated for each target frequency[2]. Optokinetic nystagmus was induced by a cloth striped drum completely surrounding the subject. The drum was turned at a constant velocity of 30 degrees/second for 30 seconds first in a clockwise then counterclockwise direction. The average velocity of the slow components in each direction was calculated[16].

Nerve conduction studies

Motor conduction velocities of the ulnar and peroneal nerves and sensory latencies of the ulnar and sural nerves on the right side were determined by standard methods[9]. Conduction velocities of slower fibers of the ulnar nerve were determined by the technique of Seppäläinen[14,13]. A Teca-4 electromyographic machine equipped with digital averager (used for sensory potentials) was used and for the double stimulus technique of Seppäläinen an additional stimulator module triggered from the first stimulator was added. This machine was used routinely in the electromyographic laboratory for clinical studies as well as subjects involved in this particular study and was calibrated at least twice weekly. All tests were performed in the controlled temperature environment of the U.C.L.A. electromyography laboratory (25 °C) and the subjects had been in the hospital for at least one to one-and-a-half hours previous to the examination and were in the EMG laboratory for at least thirty minutes prior to examination. Surface temperature was monitored and maintained at 32 °C or higher.

Audiologic testing

All testing was performed in soundproof rooms at the U.C.L.A. Clinical Audiology Laboratory by an experienced audiologist. The test battery consisted of 1) standard pure-tone air and bone conduction audiometry; 2) performance

intensity functions for phonetically balanced words (PI-PB)[8] and 3) impedance studies including tympanometry and measurement of the acoustic reflex[7]. These tests permit determination of the magnitude of hearing loss (if present) and differentiation among the possible anatomical sites of the lesion (middle ear, cochlea, eighth nerve).

RESULTS

Biochemical measurements

Table 1 lists the lead absorption measurements for both groups. All measurements were significantly different in the two groups except for plasma lead. At the time of testing approximately half of the workers had a blood lead level greater than 60 μg/100 ml and five had levels greater than 80 μg/100 ml. The mean longitudinal blood lead level for each worker was highly correlated ($r = 0.811$) with his blood lead at time of testing.

TABLE 1
Lead absorption measurements.

	Lead workers	Controls	Significance
Whole blood lead (μg/100 ml)	61.3 ± 12.8	22.0 ± 5.9	xxx
RBC lead (μg/100 ml)	144.4 ± 40.6	47.4 ± 11.4	xxx
Plasma lead (μg/100 ml)	3.4 ± 1.7	3.6 ± 0.8	n.s.
Hair lead (μg/g)	206.9 ± 192.7	12.3 ± 11.6	xxx
FEP (μg/100 ml)	235.5 ± 155.7	32.5 ± 9.5	xxx
ALA dehydratase (units/ml RBC)	123.8 ± 39.7	252.6 ± 71.7	xxx

Symptoms

Twenty-four of twenty-six neurologic symptoms covered in the questionnaire were reported more frequently by lead workers than by control workers (see reference 17 for symptoms included in the questionnaire). For 11 symptoms the differences were statistically significant at $p < 0.05$ and p values were between 0.10 and 0.05 for four additional symptom differences. The lead workers on the average reported 8.1 (± 6.7) symptoms while the control workers reported 3.8 (± 3.9) symptoms (difference significant at $p < 0.01$ level).

Neurologic examination

Decreased deep tendon reflexes (0–1+) occurred more frequently in the lead workers than in the controls. Fifteen of the 69 workers (21%) had depressed reflexes while only 11% of the controls had depressed reflexes (difference borderline significant at $p \approx 0.1$ level). Those lead workers with depressed deep tendon reflexes had significantly higher blood lead than the workers with normal deep tendon reflexes (67.4 ± 16.3 versus 59.6 ± 11.3, $p < 0.05$). There was no significant difference between lead workers and controls in the prevalence of tremor, muscle weakness, gait instability, incoordination or sensory loss (light touch, pin prick and vibration).

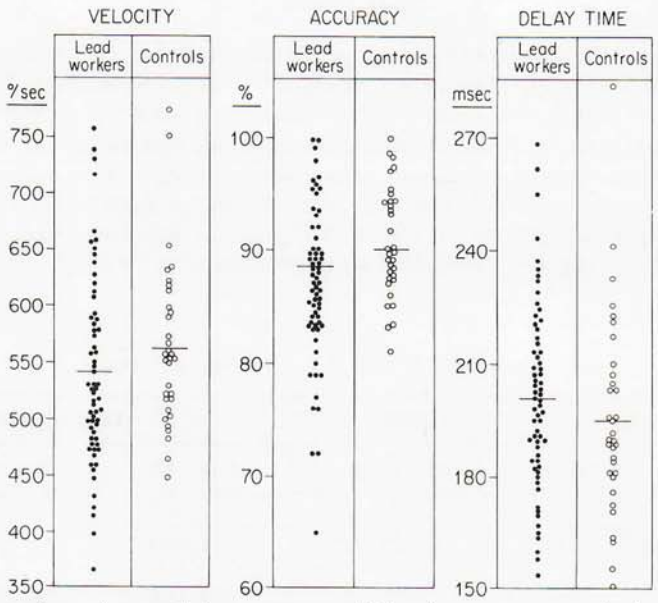

FIG. 1 – Saccade maximum velocity, accuracy and delay time measurements in the lead workers and controls. The horizontal bars represent the mean value for each group.

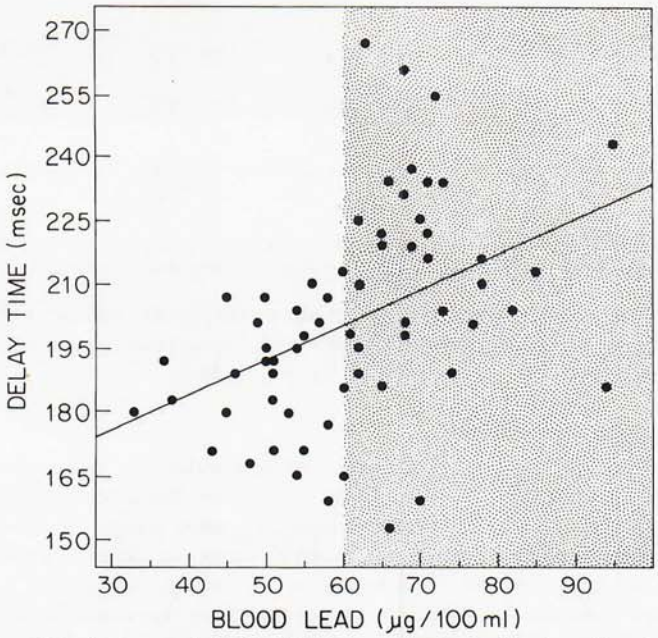

FIG. 2 – Correlation between whole blood lead concentration at the time of testing and saccade delay time in the lead workers ($r = 0.412$, $p < 0.001$).

Oculomotor studies

A comparison of saccade maximum velocity, accuracy and delay time in the lead workers and controls is shown in Figure 1. The lead workers had a lower mean velocity and accuracy and a higher mean delay time but only the accuracy measurements were significantly different in the two groups ($p < 0.05$). Smooth pursuit and optokinetic nystagmus measurements were almost identical in the lead workers and controls. Although saccade delay time was not significantly different in the two groups, as shown in Figure 2, there was a high correlation between delay time and blood lead concentration ($r = 0.412$, $p < 0.001$). Lead

TABLE 2
Nerve conduction in control and lead-exposed workers.

	Control		Lead exposed	
	Mean ± S.D.	Range	Mean ± S.D.	Range
Ulnar Motor				
– latency (msec)	3.0 ± 0.4	(2.3–3.7)	3.1 ± 0.4	(2.4–4.3)
– fast conduction (m/sec)	56.2 ± 5.5	(49–71)	55.5 ± 6.6	(38–74)
– slow conduction (m/sec)	47.3 ± 5.6	(39–59)	45.6 ± 4.8	(32–57)
Peroneal Motor				
– latency (msec)	5.1 ± 0.7	(3.9–6.6)	5.0 ± 0.9	(3.5–8.4)
– fast conduction (m/sec)	51.5 ± 5.7	(38–64)	52.1 ± 6.4	(40–79)
Ulnar Sensory				
– latency (msec)	3.2 ± 0.4	(2.6–3.9)	3.3 ± 0.6	(2.4–6.1)
Sural (Sensory)				
– latency (msec)	4.0 ± 0.4	(3.3–5.0)	3.9 ± 0.5	(3.1–6.0)

workers with a blood lead concentration above 60 μg/100 ml had a significantly higher mean saccade delay time than those with blood lead concentrations below 60 μg/100 ml (212 ± 26 versus 189 ± 16, $p < 0.001$).

Nerve conduction measurements

Table 2 summarizes the results of the nerve conduction measurements in the lead workers and controls. There were no significant differences between the two groups on standard Student's t comparisons of group means. However, several lead workers had values outside the normal range as defined by the control group. For example, seven lead workers had ulnar motor fast conduction velocities less than the 49 m/sec lower limit seen in the controls and four had ulnar motor slow conduction velocities below the lowest control value of 39 m/sec.

Only the ulnar slow conduction velocity (CVSF) was significantly correlated with the blood lead concentration at the time of testing. The correlation coefficient for the entire group was -0.274 ($p < 0.01$) and for the lead workers alone -0.274 ($p < 0.05$). Lead workers with a blood lead concentration below the 60 μg/100 ml had a meam CVSF of 46.7 ± 5.2 ($N = 31$) while those above 60 μg/100 ml had a mean CVSF of 44.6 ± 4.3 ($N = 37$) (difference significant at $p < 0.05$ level). Similar analyses of the other conduction velocity measurements did not reveal a significant difference between lead workers with blood lead levels above and below 60 μg/100 ml although the mean conduction velocity was slower in the above 60 μg/100 ml group for each measurement.

Auditory tests

The lead workers and control group did not significantly differ on any of the auditory tests. Both groups demonstrated high frequency pure tone losses consistent with the documented noise exposure. Speech discrimination was almost identical in both groups ($92.3 \pm 9.0\%$ versus $92.5 \pm \pm 6.0\%$). The stapedius reflex was present in a similar percentage of lead workers and controls and there was no difference between the two groups in reflex decay. There were no significant correlations between the indices of lead absorption and any of the auditory test results.

DISCUSSION

This report summarizes the first phase of a longitudinal study designed to identify subclinical neurologic alterations in apparently healthy lead workers with blood lead levels below 80 μg/100 ml. Lead workers and controls were intermixed so that the examiners were unaware of the status of any individual being tested. Although the lead workers complained of significantly more neurologic symptoms than the controls the neurologic examination was normal in most of the lead workers. Decreased deep tendon reflexes occurred more frequently in the lead workers but other signs of peripheral neuropathy occurred with equal frequency in both groups.

Nerve conduction velocities were not significantly different in the lead workers and controls using standard group mean comparisons. This was somewhat surprising considering two previous reports of nerve conduction slowing in lead workers with blood lead levels consistently below 80 μg/100 ml[15,11]. The levels of increased lead absorption (as measured by blood lead level at the time of testing) was higher in our study group than either of the other two study groups and the duration of employment was comparable in the three groups. One possible explanation for the differences could be the selection of the controls. Our controls were selected only from industry with similar work force characteristics while the other two studies included professionals, skilled and unskilled workers and the unemployed.

By dividing the lead workers into two groups based on blood lead concentration (below or above 60 μg/100 ml), we were able to document a significant ($p \pm 0.05$) difference in conduction velocity of slower fibers in the

ulnar nerve between the control group and the above 60 μg/100 ml group. None of the other measurements demonstrated a significant difference on similar comparisons. These findings support the observation of Seppäläinen and associates[15] that measurement of the velocity of slow conduction fibers is a sensitive technique for detecting early neurotoxic effects. The mean difference in velocity of slow conducting fibers between the control group and the workers with lead levels greater than 60 μg/100 ml was about 3 m/sec or 6% of the control value. There were no significant correlations between conduction velocity of slower fibers and clinical symptoms or signs of peripheral neuropathy. Since the average length of employment of the lead workers was 11.3 years if the conduction abnormalities were clinically important, one would have expected to find clinical evidence of neuropathy, particularly in some of the older workers.

Quantitative oculomotor function testing revealed a significant difference in saccade accuracy between the controls and lead workers and in saccade delay time between controls and the subgroup of lead workers with blood lead concentration greater than 60 μg/100 ml. Measurements of saccade velocity, smooth pursuit and optokinetic nystagmus were not significantly different between lead workers and controls. Of the five oculomotor function measurements, only saccade delay time was significantly correlated with blood lead concentration in the lead workers ($r = 0.412$, $p < 0.001$). The mean delay time of lead workers with blood lead levels greater than 60 μg/100 ml was approximately 10% higher than that of lead workers with blood lead levels below 60 μg/100 ml. It appeared that the 60 μg/100 ml level represented a breakoff point above which there was a progressive increase in saccade reaction time. The scatter in delay time measurements in both controls and lead workers however, would preclude its use as a reliable indicator of increased lead absorption in a single lead worker.

No differences in hearing were found between lead workers and controls. Pure tone levels, speech discrimination and stapedius reflex measurements were similar in both groups. Since both groups worked in an environment with high level noise exposure the frequent occurrence of high frequency hearing loss was not surprising.

In summary, relatively few differences in neurologic function were demonstrated between a group of apparently healthy lead workers from a secondary smelter and a control group from plants with similar work characteristics but no increased lead exposure. We were unable to confirm previous reports of nerve conduction slowing in lead workers with consistently low blood lead levels. The conduction velocity of slower fibers of the ulnar nerve correlated with the whole blood lead level and was significantly lower in workers with blood lead greater than 60 μg/100 ml but many of the latter group had blood lead levels greater than 80 μg/100 ml at some time in the past (five at the time of testing). The finding of impaired accuracy and delay time of saccadic eye movements in asymptomatic lead workers are new observations that require future validation. Repeat testing in the same subjects should help clarify this and other questions raised in this baseline evaluation.

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