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Relationships between lead absorption and peripheral nerve conduction velocities in lead workers

by SHUNICHI ARAKI, M.D., D.Med.Sc.,¹ and TETSUO HONMA, B.P.E.²

ARAKI, S. and HONMA, T. Relationships between lead absorption and peripheral nerve conduction velocities in lead workers. *Scand. j. work environ. & health* 4 (1976) 225—231. The motor, sensory, and mixed nerve conduction velocities of median and posterior tibial nerves were measured in 39 lead workers whose blood lead (PbB) concentrations ranged from 2 to 73 $\mu\text{g}/100\text{ g}$ with an average of 29 $\mu\text{g}/100\text{ g}$. The PbB concentrations significantly correlated with the maximal motor nerve conduction velocities (MCV) and mixed nerve conduction velocities (MNCV) of the median nerve in the forearm and with the MCV of the posterior tibial nerve. Erythrocyte δ -aminolevulinic acid dehydratase (ALAD) activity correlated similarly with the MCV and MNCV of the median nerve in the forearm, and the 24-hour urinary lead excretion following the intravenous administration of CaEDTA (20 mg/kg) (lead mobilization test) correlated with the MNCV. But no parameter correlated with the sensory nerve conduction velocities. By multiple regression analysis, a combination of the three parameters of lead absorption was found to correlate significantly with the MCV and MNCV of the median nerve in the forearm. The MCVs of the median and posterior tibial nerves in lead workers were significantly delayed in the PbB range of 29—73 $\mu\text{g}/100\text{ g}$ (mean 45), in the lead mobilization test range from 173 to 3,540 $\mu\text{g}/\text{day}$ (mean 973), and the ALAD activity range from 4.4 to 19.4 u. (mean 14.0), respectively.

Key words: lead absorption, peripheral nerve conduction velocities, lead workers, subclinical neuropathy, dose-response relationship, multivariate analysis, blood lead, lead mobilization test (with CaEDTA), δ -aminolevulinic acid dehydratase.

Motor nerve involvement of the upper and lower extremities is one of the distinguishing manifestations in "classical" lead poisoning (2), and developments in electrophysiology have made it possible to perceive diminished nerve conduction velocities in those people with symptoms of lead poisoning but no signs of neurol-

ogical involvement (3, 6, 8, 10). Recently a slight but significant slowing of motor nerve conduction velocities was revealed in lead workers without special symptoms of lead poisoning (9) and with such low levels of blood lead concentrations as $40 \pm 9\text{ }\mu\text{g}/\text{dl}$ (7). However, the direct relationships between parameters of lead absorption and nerve conduction velocities have not been confirmed previously, except in a preliminary report by one of the present authors (1).

Therefore blood lead (PbB), a lead mobilization test with CaEDTA, and erythrocyte δ -aminolevulinic acid dehydratase (ALAD) activity were selected and their relationships with nerve conduction velocities were analyzed for lead workers

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with no clinical manifestations of lead poisoning.

SUBJECTS AND METHODS

Subjects

The subjects studied were 36 male workers who had been exposed to lead occupationally from 8 months to 46 years with an average of 18 years: 24 workers in a newspaper company, 4 lead mill workers, 3 plastics workers, 2 lead smelters, 2 glass-makers, 1 batterymaker, 1 brass founder, 1 welder, and 1 plumber. The mean age was 41 years, ranging from 21 to 60 years. The mean intake of alcohol was less than 0.54 l of Sake (Japanese wine) a day for all workers except one. None of them had ever suffered from neurological, endocrinological, or renal diseases. The PbB of all the subjects ranged from 2 to 73 $\mu\text{g}/100\text{ g}$ with an average of 29 $\mu\text{g}/100\text{ g}$. Similarly the 24-h urinary lead excretion following the intravenous administration of CaEDTA (20 mg/kg) (lead mobilization test) ranged from 47 to 3,540 μg of lead/day with an average of 781 μg of lead/day for the 27 workers receiving the test; and the erythrocyte ALAD activity of 29 workers, from 4.4 to 62.3 u. (mean 23.0 u.) by the method of Weissberg et al. (11). There were no significant correlations between age and PbB ($r = -0.021$, $p > 0.25$) or between age and the other parameters.

Nerve conduction velocities

The motor, sensory and mixed nerve conduction velocities of median and posterior tibial nerves were measured at the peripheral parts of the upper and lower extremities in most of the workers and at the proximal part of the limbs in some workers in a warm laboratory (25 to 27°C). The technique for the determination of the conduction velocities is presented in the following text.

Maximal motor nerve conduction velocity (MCV). The nerves were stimulated ten times repeatedly with a couple of silver band electrodes using a supramaximal square wave pulse with a duration of 0.4 to 0.6 ms. The stimulating cathode was

placed near the nerves at three points on the right upper limb, i.e., 10 cm above the elbow, on the elbow and on the wrist, and at two points on the right lower limb, i.e., on the popliteal fossa and on the medial malleolus. The anode electrode was placed 2.5 cm distal from the same points. The muscular responses were picked up with surface electrodes taped on the belly of the thenar muscle and the abductor digiti minimi muscle in the palm and sole, respectively. The responses were amplified by the use of Sanei UB 204, averaged with an averaging data processor (Nihon Kohden ATAC 201) and then recorded on a X-Y Recorder (Yokogawa 3077). The latency of the response to the stimulation was measured from the beginning of the stimulation artifact to the first positive peak of the response or the start of the negative potential. The distance between the stimulation points was carefully measured with a tape measure. Conduction velocities were calculated for the area between the axilla and the elbow, between the elbow and the wrist, and between the knee and the ankle, respectively. For each area the distance between the two points of stimulation was divided by the difference in the latency of the response to get the velocity in m/s.

Residual latency (RL). Residual latency represents a measured period of time in excess of a calculated period of time. In this study it was calculated according to Hodes et al. (5) as follows:

$$RL = t - d/MCV,$$

where t is the time required for nerve impulses to travel from the stimulating point to the muscle; d is the distance between the stimulating point and the recording point; MCV is the maximal conduction velocity as determined in the preceding section.

Sensory nerve conduction velocity (SCV). Sensory nerves were stimulated repeatedly with a silver ring cathode, tied around the middle phalanx of the second finger, and with an anode electrode, tied 2 cm distal on the same finger, with a 60 V square wave pulse of 0.2 ms duration. The stimulating cathode was similarly tied at the base of the great toe and the anode electrode was tied 2 cm distal on the same toe. Action potentials were picked up with

Table 1. Nerve conduction velocities (m/s) and residual latency (ms) of lead workers. (MCV = maximal motor nerve conduction velocity; RL = residual latency; SCV = sensory nerve conduction velocity; MNCV = mixed nerve conduction velocity)

Conduction velocities	Number	Mean	SD
Median nerve			
MCV (axilla to elbow)	16	59.7	8.6
MCV (elbow to wrist)	38	58.1	7.6
RL	39	2.7	0.6
SCV (finger to wrist)	35	53.2	6.7
SCV (wrist to elbow)	17	59.6	4.6
SCV (elbow to axilla)	16	68.5	14.1
MNCV (wrist to elbow)	36	66.6	6.4
MNCV (elbow to axilla)	17	69.0	10.6
Posterior tibial nerve			
MCV (knee to ankle)	37	46.9	5.1
RL	37	2.3	1.2
SCV (toe to ankle)	12	48.6	3.5
SCV (ankle to knee)	10	54.6	11.8
MNCV (ankle to knee)	17	57.7	5.3

Table 2. Correlations between three parameters of lead absorption and nerve conduction velocities. [r = correlation coefficient; R = multiple correlation coefficient; R² = percentage of total variance explained by multiple regression equation (coefficient of determination)]

Conduction velocities	PbB vs conduction velocity		Mob. test ^{a, b} vs conduction velocity		ALAD ^b vs conduction velocity		PbB, mob. test ^{a, b} & ALAD ^b vs conduction velocity		
	N	r	N	r	N	r	N	R	R ²
Median nerve									
MCV (axilla to elbow)	16	-0.473	12	0.023	17	0.227	11	0.590	0.348
MCV (elbow to wrist)	38	-0.527 ****	26	-0.363	28	0.446 *	23	0.599 *	0.359
RL	39	0.076	27	-0.023	29	-0.178	24	0.343	0.118
SCV (finger to wrist)	35	-0.104	24	0.119	26	0.032	21	0.449	0.202
SCV (wrist to elbow)	17	-0.102	12	-0.352	17	0.153	12	0.411	0.169
SCV (elbow to axilla)	16	0.128	11	-0.085	16	-0.121	11	0.174	0.030
MNCV (wrist to elbow)	36	-0.451 **	24	-0.496 *	26	0.476 *	21	0.626 *	0.392
MNCV (elbow to axilla)	17	0.107	11	-0.061	17	-0.060	12	0.404	0.163
Posterior tibial nerve									
MCV (knee to ankle)	37	-0.480 ***	26	-0.375	28	0.269	23	0.451	0.203
RL	37	-0.320	27	-0.353	29	0.353	24	0.357	0.127
SCV (toe to ankle)	12	0.481	7	-0.464	13	0.040	9	0.704	0.496
SCV (ankle to knee)	10	0.095	6	-0.693	10	-0.180	6	0.778	0.605
MNCV (ankle to knee)	17	-0.211	13	-0.207	17	0.315	12	0.386	0.149

^a Lead mobilization test with CaEDTA.

^b Transformed into logarithm.

* p < 0.05; ** p < 0.01; *** p < 0.005; **** p < 0.001.

surface electrodes at the wrist, elbow, axilla, ankle, and knee. The conduction velocities were calculated for the areas between the finger and the wrist, between the wrist and the elbow, between the elbow and the axilla, between the toe and

the ankle, and between the ankle and the knee, respectively.

Mixed nerve conduction velocity (MNCV). A supramaximal square wave pulse of 0.2 ms duration was applied at the wrist and the ankle with the recording electrodes set for the measurement of SCV. Nerve action potentials were then recorded at the elbow, axilla and knee levels. The conduction velocities were calculated for the areas between the wrist and the elbow, between the elbow and the axilla, and between the ankle and the knee, respectively.

Precision and accuracy of the measurements of nerve conduction velocities

The nerve conduction velocities were measured for 10 successive days in a 22-year-old university student. When expressed as a coefficient of variance (standard deviation/mean value), the daily variations of the nerve conduction velocities were as follows: MCV (axilla to elbow), 10.1 %; MCV (elbow to wrist), 3.5 %; RL (palm), 9.6 %; SCV (finger to wrist), 3.5 %; SCV (wrist to elbow), 5.6 %; SCV (elbow to axilla), 10.2 %; MNCV (wrist to elbow), 4.5 %; MNCV (elbow to axilla), 7.8 %; MCV (knee to ankle), 3.0 %; RL (sole), 10.4 %; SCV (toe to ankle), 5.4 %; SCV (ankle to knee), 5.0 %; and MNCV (ankle to knee), 8.6 %.

The conduction velocities measured in 39 "healthy" men without any particular exposure to neurotoxic chemicals or a history of peripheral neuropathy were as follows: MCV (elbow to wrist), 58.3 ± 4.7 m/s; MNCV (wrist to elbow), 68.3 ± 4.8 m/s; MCV (knee to ankle), 49.5 ± 5.5 m/s. There were no significant differences in the conduction velocities between 23 non-drinkers and 15 drinkers up to 0.54 l of Sake a day.

Analysis of blood and urinary lead concentrations and erythrocyte ALAD activities

Blood and urinary lead concentrations were determined by atomic absorption spectrophotometry (Perkin—Elmer 403) with a procedure of wet ashing, chelation by ammonium pyrrolidine dithiocarbamate

Fig. 1. Relationships between parameters of lead absorption and maximal motor nerve conduction velocities (MCV) of the median nerve in the forearm and of the posterior tibial nerve.

and extraction to water-saturated isobutylmethylketone. Erythrocyte ALAD activities were measured by the aforementioned method of Weissberg et al. (11). The ALAD activity of one unit corresponds to 0.03 μ mole porphobilinogen per milliliter of packed red blood cells per hour in this method.

The accuracy of the measurements of blood and urinary lead concentrations was tested several times by double analysis with the Occupational Health Service Center of the Japan Industrial Safety Association, and the results were satisfactory. The reproducibility of the determinations of urinary lead was 8.2 %, when expressed as a coefficient of variance.

The mean value of PbB was 12 μ g/100 g in 25 male adults free from occupational exposure to lead; that of the lead mobilization tests, 95 μ g/day; and ALAD, 39.7 u. Similarly, the upper 95 % confidence limits of PbB and the lead mobilization test were 25 μ g/100 g and 170 μ g/day, respectively, the lower 95 % confidence limit of erythrocyte ALAD activity being 20 u.

Statistical analysis

Multiple linear regression analysis was performed by the use of a Hitac 8700 at the University of Tokyo.

RESULTS

The nerve conduction velocities measured are listed in table 1. The relationships between the three major parameters of lead absorption and conduction velocities are shown in table 2. The MCV of the median nerve in the forearm correlated significantly with the PbB level and the erythrocyte ALAD activity; and the MCV of the posterior tibial nerve, with the PbB level (fig. 1). Similarly, the MNCV of the median nerve in the forearm correlated with the PbB concentration, the lead mobilization test, and the ALAD activity (fig. 2). However, the SCVs did not correlate with any parameter (table 2).

When the three parameters of lead absorption were analyzed for the nerve conduction velocities by multiple regression analysis, the three parameters combined significantly correlated with the

Fig. 2. Relationships between parameters of lead absorption and mixed nerve conduction velocities (MNCV) of the median nerve in the forearm.

MCV and MNCV of the median nerve in the forearm (table 2).

The MCV and MNCV of the median nerve in the forearm and the MCV of the posterior tibial nerve are compared between lead workers and age-matched "healthy" people in table 3. When lead

Table 3. Significant levels of diminished nerve conduction velocities in lead workers. (MCV = maximal motor nerve conduction velocity; MNCV = mixed nerve conduction velocity)

Conduction velocities	Lead workers PbB 29—73 (45 ^a) $\mu\text{g}/100\text{ g}$			Control subjects			Level of significance
	N	Mean	SD	N	Mean	SD	
MCV (elbow to wrist)	19	54.3	6.0	19	59.0	2.9	$p < 0.01$
MCV (knee to ankle)	19	44.7	5.0	19	50.0	6.2	$p < 0.01$
MNCV (wrist to elbow)	19	64.1	5.7	19	67.1	3.6	$p > 0.05$

Conductions velocities	Lead workers Lead mobilization test 0.17—3.54 (097 ^a) mg/day			Control subjects			Level of significance
	N	Mean	SD	N	Mean	SD	
MCV (elbow to wrist)	20	54.6	6.2	20	59.5	3.3	$p < 0.01$
MCV (knee to ankle)	21	45.9	5.7	21	49.5	5.6	$p < 0.05$
MNCV (wrist to elbow)	21	65.2	6.5	21	67.5	3.6	$p > 0.05$

Conduction velocities	Lead workers ALAD 4.4—19.4 (14.0 ^a) u.			Control subjects			Level of significance
	N	Mean	SD	N	Mean	SD	
MCV (elbow to wrist)	15	54.3	6.1	15	58.4	2.4	$p < 0.05$
MCV (knee to ankle)	15	43.8	5.1	15	49.4	5.8	$p < 0.01$
MNCV (wrist to elbow)	15	64.1	5.9	15	68.0	2.5	$p < 0.05$

^a Mean value.

workers with PbB values above the upper 95 % confidence limit in nonexposed male adults are chosen, their MCVs in the forearm and leg are significantly delayed in the range of PbB from 29 to 73 $\mu\text{g}/100\text{ g}$ (mean 45 $\mu\text{g}/100\text{ g}$) on a group basis. Similarly the MCVs are significantly delayed in the ranges of the lead mobilization test from 173 to 3,540 $\mu\text{g}/\text{day}$ and ALAD activities from 4.4 to 19.4 u., respectively.

DISCUSSION

The significant correlations of the PbB, concentrations and the lead mobilization tests with conduction velocities indicate the existence of a dose-effect relationship for lead in workers with PbBs below 73 $\mu\text{g}/100\text{ g}$. The close relationship between conduction velocities and ALAD activities, whose inhibition is measurable in vitro at

about 10 to 20 μg of lead/dl of blood and reaches a maximum at 70 to 90 μg of lead/dl (4), shows that the influence on conduction velocities starts at such a low level of the human body burden of lead. And the multiple regression analysis confirmed more definitely the relationship between lead absorption and the slowing of nerve conduction velocities.

This relationship does not mean, however, that a significant decrease in conduction velocities occurs on an individual level. Since the lower limit of the MCV of the median nerve in the forearm was 48.9 m/s in "healthy" people, only 5 out of 19 workers with PbBs between 29 and 73 $\mu\text{g}/100\text{ g}$ showed diminished MCVs (fig. 1). This finding suggests that a slight delay in nerve conduction velocities occurs in about 26 % of lead workers at PbB levels of about 45 $\mu\text{g}/100\text{ g}$.

The delay in the conduction velocities and the correlations with parameters of

lead absorption were the most significant for the motor nerves, but the same trends were also found for mixed nerve conduction velocities. Although sensory nerve conduction velocities remained unchanged in all parts of the upper and lower extremities, the involvement of the fastest sensory nerve fibers may not be excluded.

So far as the parts of the upper and lower extremities are concerned, the conduction velocities seemed to be affected mainly in the forearm. The topographical findings seem to be qualitatively similar to the clinical observations that wrist drop is the most frequent phenomenon among muscular paralysis in classical lead poisoning. The topographical nature might have played an important part in the development of localized lead palsy, as well as in predisposing factors such as fatigue (2). Although it is not obvious in the present study if the motor nerve conduction velocity is affected in the palm, the diminished MCV of the median nerve in the forearm may be a manifestation of motor peripheral neuropathy due to lead absorption. The motor nerve involvement in the leg may be consistent with the clinical observation that the paralysis of the lower extremities occurs, though less frequently, in "classical" lead poisoning (2).

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