Sensitive technique for detecting subclinical lead neuropathy

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Seppäläinen, A. M., and Hernberg, S. (1972). *Brit. J. industr. Med.*, **29**, 443-449. **Sensitive technique for detecting subclinical lead neuropathy.** Subclinical neuropathy was studied in 39 male lead workers. Although 31 had a diagnosis of poisoning, all were without clinical signs of neurological impairment. A standard electromyogram revealed abnormalities (fibrillations and/or diminished number of motor units) in 24 men. The mean maximum conduction velocities (MCV) of the ulnar and median nerve were significantly lower in the group of lead workers as compared with an age-matched control group. Measurement of the conduction velocity of the slower fibres (CVSF) of the ulnar nerve proved to be a very sensitive indicator of lead damage. This measurement was done as a modification of Hopf's technique using a partial antidromic block. A combination of this variable and the distal latency of the median nerve discriminated lead workers from controls better than any other combinations. The findings are consistent with slight neuropathy. They further show that lead also affects certain portions of the fibres in the proximal part of the nerve.

The neurophysiological findings of the lead workers were collated to form a neurophysiological score (NF score). This score was used to compare the neurophysiological state with the degree of present lead effect, as judged from a rigid classification based on defined subjective symptoms and results of laboratory tests. There was poor agreement between the severity of lead effect and the NF score. No isolated laboratory test correlated with the neurophysiological findings.

From these results it appears that subclinical nerve damage can be detected in lead workers with no clinical neurological symptoms. Measurement of the CVSF is a particularly sensitive method for this purpose. The lack of correlation between the severity of subclinical nerve damage and the intensity of lead effect, as judged by commonly used criteria, suggests that nerve damage is produced independently of other manifestations of poisoning. This observation indicates the need for further studies on the value of present acceptable limits of lead exposure from the point of view of the nervous system.

Improvements in occupational hygiene together with regular medical supervision of exposed workers have caused a drastic reduction in severe neurological manifestations of industrial lead poisoning during the last decades, but this does not rule out the possibility of subclinical nerve damage. However, few studies dealing with this problem have been published.

Using electrophysiological techniques, Sessa, Ferrari, and Colucci D'Amato (1965) were able to show reduction of the maximal motor conduction velocity (MCV) of the ulnar nerve in some patients with lead poisoning without clinical neurological symptoms. Catton, Harrison, Fullerton, and Kazantzis (1970) made an electrophysiological study of five patients with lead poisoning and another 14

men with heavy occupational exposure. None had clinical neurological abnormalities. The mean MCV of the lateral popliteal nerve of the exposed men did not differ from that of an unexposed control group, but several exposed subjects had a diminished ratio of the muscle action potential amplitudes following stimulation at the knee and at the ankle. The conclusion was that although the MCV was normal, conduction was slowed in some fibres and this caused a dispersal of the muscle action potential.

Since the MCV remains normal as long as a portion of the fastest fibres is intact, more sensitive methods are obviously needed to detect early or partial damage in peripheral nerves. We have tried to develop such methods and to evaluate their usefulness in lead poisoning. The present paper reports on these studies.

Material and methods

Subjects

The exposed group comprised 39 male lead workers. Their mean age was 36.1 years with a standard deviation of 11.7 (range 18 to 63 years). They had been exposed for periods ranging from 2.5 months to 22 years. A diagnosis of lead poisoning (class I to III, see later) was made in 31 cases. The remaining eight men had excessive or increased absorption but were without symptoms of poisoning at the time of examination. On some previous occasion, 15 of the men suffering from lead poisoning in this study and five of the symptom-free men had suffered from clinical lead poisoning. Seventeen of the subjects came from two lead scrap smelteries, seven from a polyvinyl-chloride plastic plant, and five from two storage battery factories. Another five were engaged in ship-breaking and three in welding and repair of sulphuric acid containers. The remaining two had been mixing red lead (Pb_3O_4) into crystal glass mass.

According to measurements made during the last three years, the concentration of lead in the air of the lead smelteries was some 10 to 20 times the threshold limit value of 0.2 mg/m³. Similarly, poor conditions prevailed in one of the accumulator factories. The other showed concentrations around 0.2 mg/m³. No measurements had been performed in the other work-places. Use of personal protective equipment was common.

Other diseases or conditions that could cause neuropathy were excluded in all cases. Special attention was given to the exclusion of alcoholism, diabetes, renal failure, neurological diseases, and exposure to toxic solvents. All electrophysiological measurements were performed either before the start or during the two first days of chelation therapy, if given.

Classification of degree of lead absorption

To provide a basis for comparisons between the neurophysiological findings and the severity of lead absorption and/or poisoning, we tried to group the subjects into five well-defined categories. One of us (S.H.) made the classification without any knowledge of the neurophysiological findings. The criteria were as follows:

Class I Severe clinical poisoning Any of the following symptoms or signs in combination with symptoms belonging to class II and III and/or laboratory results of class IV:

- colic (severe abdominal cramps of intermittent nature)
- diffuse abdominal pain (daily for at least 2 weeks)
- paresis or paralysis (not found in a single case)
- encephalopathy (not found in a single case).

Class II Moderate clinical poisoning Clinical poisoning without the symptoms of class I. At least three of the following symptoms together with the symptoms of class III and the laboratory results of class IV:

- diffuse abdominal pain (daily for less than two weeks or occasionally for any longer period)
- nausea (regular indigestion and/or occasional vomiting)
- constipation (no defaecation for three days or more, or very hard stools for one week or more)
- weight loss (= 3 kg)
- headache (for at least three days per week)
- distinct general fatigue or somnolence
- muscular exhaustibility
- tremor
- myalgia, paraesthesiae, arthralgia
- anaemia (haemoglobin below 11 g/100 ml, other causes excluded).

Class III Mild clinical poisoning Absence of symptoms and signs of class I. Less than three of the symptoms and signs of class II and/or any of the following symptoms and signs in combination with the laboratory results of class IV:

- occasional abdominal discomfort
- mild fatigue or muscular exhaustibility
- uncertain myalgia or paraesthesiae
- slight anaemia (haemoglobin 11-13 g/100 ml).

Class IV Excessive absorption No subjective symptoms. Haemoglobin <13 g/100 ml. One or both of the following laboratory tests positive:

- blood lead more than 80 µg/100 ml
- urinary ALA more than 25 mg/l.

Class V Increased absorption No subjective symptoms. One or both of the following findings:

- blood lead 40-80 µg/100 ml
- urinary ALA 10-25 mg/l.

The distribution of subjects into different classes is shown in Table 2. None had objective clinical neurological abnormalities.

Controls

The controls were pair-matched for age with the exposed subjects. Of the 39 men used as controls, 16 were college or university graduates (physicians, psychologists, engineers) and 23 were skilled or unskilled workers (farmers, drivers, mechanics, manual labourers). None of the controls had had any known exposure to lead or other toxic industrial agents. There were no indications of neurological disease.

Laboratory methods

The concentration of lead in whole blood was determined from duplicate samples after wet oxidation using a

dithizone method (Keenan, Byers, Saltzman, and Hyslop, 1963), urinary δ -aminolaevulinic acid (ALA) according to Grabecki, Haduch, and Urbanowicz (1967), and haemoglobin using routine methods.

Electrophysiological methods

A standard electromyographic (EMG) examination was performed on all exposed subjects, using a Disa electromyograph and concentric needle electrodes. At least one wrist extensor and one intrinsic hand muscle were always examined; in all, from four to eight muscles were studied. No needle electrode EMG was performed on the controls. The patterns of maximal contraction, shape, duration, and amplitude of single motor units, as well as possible spontaneous activity during muscular relaxation, were noted.

Maximal motor conduction velocity The MCV of the median, ulnar, and lateral popliteal nerves was measured for all exposed subjects and controls with the standard method (Hodes, Larrabee, and German, 1948). The room temperature was 25°C to 26°C and the skin temperature at the proximal stimulation point 31.5°C to 34°C in the arms and 31.5°C to 33.5°C in the legs. The nerves were stimulated with a skin electrode at two points (arms at elbow level and at 2 cm above the wrist fold; legs—just above the head of the fibula and at the ankle) along the course of the nerve with supramaximal square wave stimuli of 0.3 to 1.0 ms duration from a Disa Multistim. The muscular response was recorded with skin electrodes taped on the belly and tendon of the opponens pollicis, the abductor digiti minimi, and the extensor digitorum brevis muscles. The responses were amplified with the

electromyograph. The latencies were determined using a Telequipment oscilloscope with the aid of the Multistim potentiometer. The distance in millimetres between the stimulation points was carefully measured with a tape-measure.

Conduction velocity of slower fibres (CVSF) This was measured using a partial antidromic block. This technique, developed by one of us (Seppäläinen 1971), is a modification of the method first described by Hopf (1962). The principle is as follows: If the nerve is simultaneously stimulated at two different points, the antidromic volley from the distal stimulus point stops the orthodromic volley from the proximal point on its way to the muscle. Thus only one muscular response is obtained, i.e., that corresponding to the distal stimulus. If, on the other hand, the proximal stimulus is sufficiently delayed, two successive muscular responses, corresponding to each of the stimuli, can be recorded. The interval between the stimuli is then gradually shortened until the second response begins to decrease. Some fibres are now being inhibited by the antidromic volley although most of them are still conducting the impulse. The latency of the slow fibres between the stimulation points is obtained by subtracting 1 ms (the refractory period of the nervous fibres) from the shortest interval between paired stimuli with full response. The CVSF can then be calculated by dividing the distance by the latency time.

According to a pilot study, the CVSF is the same in the right and the left arms. Because of this, we studied only the right ulnar nerve. The experimental arrangement is shown in Figure 1. The first stimulus point was at wrist level and the second on the distal part of the upper

FIG. 1. The experimental arrangement for measurement of the CVSF of the right ulnar nerve.

- S_1 } stimulating electrodes
- S_2 } (stimulus artefacts in the insert)
- M_1 = muscular response to S_1 ;
- M_2 = muscular response to S_2 ;
- d = different electrode
(on the belly of the abductor digiti minimi)
- i = indifferent electrode
(on the tendon of the abductor digiti minimi).

TABLE 2
SOME DATA ON THE EXPOSED SUBJECTS

Degree of lead effect	Case no.	Age	Neurophysiol. findings ¹							NF score	Previous poisoning
			1	2	3	4	5	6	7		
Class I Severe clinical poisoning	33	25	1	1		1			1	4	+
	2	58			1	1		1		3	+
	6	50		1	1	x				x	+
	26	35				x	1	1	1	x	+
	23	43				1			1	2	+
	5	53		1		2		1	2	6	-
	27	25							1	1	-
	17	23								0	-
	18	30			1	2		1		4	+
	16	41			1	x			1	x	+
Class II Moderate clinical poisoning	21	44					1			1	+
	1	23		1	1		1	1	1	5	-
	20	21				2		1		3	-
	24	28				1		1		3	-
	22	18							1	1	-
	4	25							1	1	-
	11	37				1				1	-
	15	31				1				1	-
	39	30								0	-
	38	63	1	1	1	1	1	1	2	8	+
Class III Mild clinical poisoning	19	27		1	1	1		1	1	5	+
	37	60		1	1	1			1	4	+
	25	48		1	1	x	1			x	+
	30	28		1	1	x	1			x	+
	34	35		1						1	+
	31	26		1	1			1		3	-
	7	35	1			1				2	-
	13	22		1					1	2	-
	29	28				1		1		2	-
	32	23				x	1			x	-
Class IV Excessive absorption	28	35								0	-
	12	46				1		1	2	4	+
	8	35						2		2	+
Class V Increased absorption	14	26				x		1		x	+
	36	54			1	1	1		2	5	+
	10	43								0	+
	9	38						1		1	-
	3	39								0	-
	35	35								0	-

¹The numbers of the columns under 'neurophysiol findings' correspond to those in Table 1. The CVSF (column 4) of seven subjects was not measured. Missing data are indicated by x.

in the peripheral nerves of 15 baboons poisoned with lead. This was verified by histological examination, EMG, and measurements of the nerve conduction velocity. The nature of lead palsy in man still remains obscure (Hopkins, 1970). Although Simpson, Seaton, and Adams (1964) believe that neuronopathy of the anterior horns is the cause of lead palsy, the findings

of Sessa and his colleagues (1965), as well as those of Catton and his co-workers (1970), are all more compatible with peripheral neurogenic lesions, most likely peripheral neuropathy. We are inclined to agree with the latter authors, since our results suggest segmental demyelination with partial damage of the nerve trunks.

FIG. 2. NF score and present lead effect. For classification of the lead effect, see text.

Lead workers A = first episode of excessive absorption or poisoning

Lead workers B = subjects with one or more previous episodes of lead poisoning

FIG. 3. CVSF of the right ulnar nerve in lead workers A, lead workers B, and normal controls.

The animal experiments cited above (Fullerton, 1966; Schlaepfer, 1969) suggest that the segmental demyelination involves only some of the nerve fibres. Because measurement of the MCV is rather insensitive, more refined techniques are needed for demonstrating such damage. The method used by Catton and his team (1970) is an improvement, but still more sensitivity can be obtained by measuring the distal latency of the median nerve and, especially, the CVSF of the ulnar nerve using a partial antidromic block. Both these measurements are technically simple and fairly quick to perform. One problem is that a refractory period of 1 ms used in the calculations of the CVSF may be slightly too short for the most abnormal cases. Thus the slowest CVSF values measured may seem a little too patho-

logical. But in these cases the true CVSF would be far from the normal range anyhow. Measuring the actual refractory period in each subject would, of course, have added to accuracy. However, as the practical significance would have been questionable, we considered it justified to simplify our technique and leave out this cumbersome procedure.

Our results specifically revealed that the slower nerve fibres are being damaged by lead. Moreover, some fibres are damaged not only in the distal part of the nerve, which is known to be vulnerable to noxae of different origins, but also in its proximal part. Another notable finding in concordance with neurogenic lesions was the abundance of EMG abnormalities, i.e., fibrillations and a diminished number of motor units.

TABLE 3
NERVE CONDUCTION VELOCITY FINDINGS IN 39 LEAD WORKERS AND 39 AGE-MATCHED CONTROLS

Variable	Mean $\pm$ S.D.		T	P
	Exposed	Controls		
Age (yr)	36.1 $\pm$ 11.7	35.5 $\pm$ 11.5		
MCV (m/s) of the median nerve	55.3 $\pm$ 3.7	58.6 $\pm$ 3.7	4.00	< 0.001
Distal latency (ms) of the median nerve	4.6 $\pm$ 0.6	4.0 $\pm$ 0.5	5.10	< 0.001
MCV (m/s) of the ulnar nerve	54.0 $\pm$ 5.2	56.7 $\pm$ 3.4	2.84	< 0.01
CVSF (m/s) of the ulnar nerve ¹	39.0 $\pm$ 8.0	46.6 $\pm$ 3.7	4.90	< 0.001
MCV (m/s) of the lateral popliteal nerve	48.4 $\pm$ 5.1	50.7 $\pm$ 3.6	2.30	< 0.025

¹Data from 32 exposed subjects and 32 controls

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