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Relationship between clinical and electrophysiological findings and indicators of heavy exposure to 2,3,7,8-tetrachlorodibenzo-dioxin.

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Relationship between clinical and electrophysiological findings and indicators of heavy exposure to 2, 3, 7, 8 - tetrachlorodibenzo-dioxin

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FILIPPINI G, BORDO B, CRENNA P, MASSETTO N, MUSICCO M, BOERI R. Relationship between clinical and electrophysiological findings and indicators of heavy exposure to 2,3,7,8-tetrachlorodibenzo-dioxin. *Scand j work environ health* 7 (1981) 257—262. In this study the prevalence rate of peripheral neuropathy in a population living in an area polluted with 2,3,7,8-tetrachlorodibenzo-dioxin (dioxin-TCDD) was determined. Of the 723 subjects invited to the first screening in 1977, 470 (65 %) attended. At the second screening in 1978, of the 710 invited subjects, 319 (45 %) attended. Prevalence rate ratios for peripheral neuropathy and the associated 95 % confidence limits were calculated for subgroups determined by the presence of (i) predisposing factors to neuropathy (alcoholism, diabetes, occupational exposure to neurotoxic agents, etc) or (ii) conditions thought to result from exposure to dioxin-TCDD such as chloracne or abnormal serum hepatic enzyme levels. The prevalence rate of peripheral neuropathy among those subjects with predisposing factors and among those with chloracne or abnormal serum hepatic enzyme levels was nearly three times greater than among those without these manifestations. The results derived from this study may be useful qualitative pointers for identifying subjects at risk in the neurological follow-up.

Key terms: chloracne, dioxin, environmental pollutants, liver damage, peripheral neuropathy, raised serum hepatic enzyme levels.

Subjects with occupational or accidental exposure to 2,3,7,8-tetrachlorodibenzo-dioxin (dioxin-TCDD) have been found to develop a wide variety of lesions and symptoms. Neurological findings may include polyneuropathies, lower extremity weakness, or sensorial impairment (sight, hearing, smell, taste), all of which have been recorded for dioxin-exposed subjects in whom other long-term effects such as chloracne, raised levels of cholesterol, triglyceride, gamma-glutamyl transpeptidase (γGT), glutamic oxalacetic transaminase (GOT), and glutamic pyruvic transaminase (GPT) were manifest (1, 3, 6, 7, 10, 11, 12, 13, 14, 17, 18). An association of chloracne with increased γGT, GOT, and GPT activities and abnormal lipid levels has also been reported (19, personal communication from M Moses). The rate of reported congenital anomalies in men fathering at least one child after service in Viet Nam was nearly twice as high among those with recurrent acne, skin rash with blisters, and skin color changes consistent with conditions thought to result from exposure to dioxin-contaminated substances as among those without them (15). For men with these "indicators of exposure" greater frequencies have also been reported for gastrointestinal disturbances, swelling or numbness of joints, and sleep and psychological disturbances (15).

These previous findings prompted us to compare the prevalence rate (PR) of peripheral neuropathy in exposed subjects

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with chloracne or increased γGT, GOT, and GPT activities with that found in exposed subjects without these manifestations in a population living in a dioxin-polluted area in the Seveso region of Italy.

Subjects and methods

In July 1976, an accident at a trichlorophenol-producing factory in Meda, Italy, resulted in the contamination of a large, densely populated area. Seven hundred and thirty-three residents were evacuated 15 to 20 d after the accident from the most polluted zone (an area of 108 ha with an average dioxin-TCDD level of 240 $\mu g/m^2$, a maximum level of 5,477 $\mu g/m^2$, and an unevaluable minimum level) (4). These residents were invited by letter and personal invitation during visits at home to an initial neurological screening in March 1977 and to a second screening in April 1978. At the first screening five subjects had died and five had moved from the area. Of the 723 inhabitants invited to participate in the screening in Seveso, 470 (65 %) attended. During the period March 1977 to April 1978, five died and nine moved from the area. Of the 709 inhabitants invited to the second screening, 319 (45 %) attended, 277 of whom had been examined at the first screening and 42 of whom were examined for the first time. Of the latter 42, 11 children under the age of 5 a refused to participate in the electrophysiological examination and were thus excluded from the prevalance calculation. No acute polyneuropathy was found during the study.

Each subject was examined according to a standardized protocol requiring a medical history questionnaire, a clinical examination, and an electrophysiological investigation. The neurological symptoms specifically identified were paresthesia, hypesthesia, pain, and hyposthenia, and the clinical signs were superficial and deep sensory impairment, muscular weakness, and tendon hypo- or areflexia. The electrophysiological study included maximum and minimum motor conduction velocity along the ulnar (axilla-wrist) and peroneal (capitulum fibulae-ankle) nerves and needle electromyography on the first interosseous muscle. However, electromyography was abandoned during the course of the study because many subjects rejected the use of the needle. Muscle action potentials were recorded by a superficial electrode (Disa 13 K 60) from the digit minimum abductor and extensor digitorum brevis muscles at a surface temperature above 27°C. Minimum conduction velocity was determined by the desynchronization method of Cosi et al (5). Motor distal latencies were corrected to a standard distance of 6 cm. A Disa 1500 electromyograph (Disa Elektronik, Skovlunde, Denmark) was used.

A nonexposed population living in an unpolluted area was used as a source for "normal" reference values of the electrophysiological parameters. A total of 380 (91.6 % of the randomized sample) subjects, representative of all ages, participated. Seventy-five of these subjects were alcoholic, occupationally exposed to neurotoxic agents, or had diseases predisposing to peripheral neuropathy and were thus excluded from the calculation of the reference values. The "normal" reference values obtained are given by age groups in table 1. Conduction velocity and distal latency were considered to be in the pathological range when the former was lower than the mean — 2 SD and the latter was higher than the mean + 2 SD of the reference population of the same age group. These two parameters were normally distributed. Amplitude and duration of muscle action potential were considered abnormal when the former was below the lower range limit and the latter was above the upper range limit of the reference population of the same age group.

For an electrophysiological diagnosis of peripheral neuropathy two or more abnormal parameters, among which conduction velocity was obligatory, were considered necessary, regardless of the involved nerve. All Seveso subjects were investigated for the following factors predisposing to neuropathy: alcoholism (more than 1 l of wine consumed daily), personal history of diabetes or fasting plasma glucose $\geq$ 100 g‰, cancer, nutritional deficiency, infectious and inflammatory diseases, osteoarticular diseases, use of neurotoxic drugs, possible occupational exposure to neurotoxic agents [chemical workers, shoemakers, plastic workers, painters, cabinet makers, printers, tanners, ceramic work-

ers — according to the International Standard Classification of Occupations (9)]. Chloracne was diagnosed by a dermatologist.

Increased enzyme activities were recorded when γGT was above 50 U/l (normal range: up to 36 U/l, as determined according to Szasz [16]), GOT was above 50 U/l [normal range: up to 26 U/l, as determined by the "optimized method" (2)], and GPT was above 50 U/l [normal range: up to 32 U/l, as determined by the "optimized method" (2)].

The statistical analysis of the data was performed within the exposed population, the relationship between peripheral neuropathy and indicators of heavy exposure to dioxin being tested. The PR and the prevalence rate ratio (PRR) of peripheral neuropathy were calculated for the Seveso subjects with chloracne or raised serum hepatic enzyme levels versus Seveso subjects without them. Ninety-five percent confidence limits (95 % CL) were estimated according to the method described by Woolf (20).

Results

Relationship between the occurrence of peripheral neuropathy and indicators of heavy exposure to dioxin

By 31 June 1977, 22 cases with symptoms or clinical and electrophysiological signs of peripheral neuropathy and 20 cases with electrophysiological abnormalities had been found among the 470 subjects examined, for a total PR of 8.9 % (95 % CL, 6.2—11.6). Among the 308 subjects who underwent a complete examination, 26 cases with symptoms or clinical and electrophysiological signs of peripheral neuropathy and 16 cases with electrophysiological abnormalities were found by 31 July 1978, for a total PR of 13.6 % (95 % CL, 9.5—17.8).

Table 2 reports the PR and the PRR of peripheral neuropathy for subjects with predisposing factors (group A) and for subjects with chloracne or raised serum hepatic enzyme levels (group B) versus subjects without the symptoms of either

Table 1. Motor conduction velocity, distal latency, amplitude, and duration of muscle action potential (surface electrodes) in the 305 referents.

Nerve	Number of referents	Age (a)	Maximum conduction velocity (m/s)		Minimum conduction velocity (m/s)		Distal latency (ms)		Amplitude (mV)	Total duration (ms)
			Mean ± SD	Median	Mean ± SD	Median	Mean ± SD	Median	Range	Range
Ulnaris	172	6—29	60.2 ± 5.3	60	55.5 ± 6.1	55	2.5 ± 0.6	2.5	4.5—15	11—19
(axilla-	118	30—59	58.2 ± 4.4	58	54.3 ± 4.3	55	2.5 ± 0.5	2.5	4.5—15	11—19
wrist)	15	≥ 60	57.9 ± 5.0	57	53.4 ± 4.4	52	2.6 ± 0.5	2.6	4.5—15	11—19
Peroneal	168	6—29	52.7 ± 5.0	52	48.9 ± 4.9	49	3.0 ± 0.5	3.1	2—11	10—17
(capitulum	115	30—59	50.9 ± 4.1	51	47.9 ± 3.7	47	3.3 ± 0.8	3.2	2—11	10—17
fibulae-	12	≥ 60	49.8 ± 3.7	50	47.3 ± 4.1	47	3.9 ± 0.6	3.4	2—11	10—17
ankle)										

Table 2. Prevalence rate (PR) and prevalence rate ratios (PRRs) for peripheral neuropathy in subgroups of Seveso residents in 1978.

	A With predisposing factors	B With indicators of exposure	C Without A or B
Actual cases of peripheral neuropathy	17	12	13
Total number of subjects	85	55	168
PR (%)	20	22	7.7
PRR [a]	2.6	2.8	1
95 % confidence limits	1.2—5.6	1.2—6.5	

[a] Evaluated versus group C.

group A or B (group C). For the subjects of group A the PRR was significantly greater than one, as one would expect. The PRR was significantly greater than one also for the subjects of group B.

Table 3 shows the PRR of peripheral neuropathy for subjects with increased γGT, GOT, and GPT activities and for subjects with chloracne versus subjects without any of these manifestations. The PRR was significantly different from one for the subjects with abnormal hepatic enzyme levels and was greater than one for the subjects with chloracne, even though the lower 95 % CL was equal to one.

Relationship between clinical symptoms and signs and peripheral neuropathy

Clinical symptoms and signs (paresthesia, hyposthenia, weakness, hypo- or areflexia in the upper and lower limbs) were significantly associated with peripheral neuropathy in the three subgroups of the exposed population (table 4). Six subjects with symptomatic neuropathy and six with asymptomatic neuropathy and six with clinical symptoms and signs only, without electrophysiological evidence of peripheral neuropathy, were found in the group with indicators of heavy exposure to dioxin. The arms and legs were involved for six polyneuropathic subjects with chloracne or raised serum hepatic enzyme levels, the legs of one and the arms of five (the last five subjects were children with chloracne).

Discussion

It is evident from the preceding results that a very high prevalence of peripheral

Table 3. Prevalence rate ratios for peripheral neuropathy in Seveso subjects with chloracne or abnormal hepatic enzyme levels in 1978.

	Abnormal hepatic enzyme levels [a]		Chloracne [a]	
	With	Without	With	Without
Actual cases of peripheral neuropathy	6	19	6	19
Total subjects	18	205	24	199
Prevalence rate ratio	3.6		2.6	
95 % confidence limits	1.3—10.2		1.0—7.2	

[a] Calculated only for subjects without predisposing factors to peripheral neuropathy.

Table 4. Relationship between clinical symptoms and signs and peripheral neuropathy in subgroups of Seveso residents.[a]

Subjects	A With predisposing factors				B With indicators of exposure				C Without A or B			
	Symptoms and signs		No symptoms or signs		Symptoms and signs		No symptoms or signs		Symptoms and signs		No symptoms or signs	
Neuropathic	11	(65) [30]	6	(35) [12]	6	(50) [50]	6	(50) [14]	9	(69) [60]	4	(31) [3]
Normal	26	(38) [70]	42	(62) [88]	6	(14) [50]	37	(86) [86]	6	(4) [40]	149	(96) [97]
	$\chi^2 = 3.88$		$p < 0.05$ [b]		$\chi^2 = 7.15$		$p < 0.01$		$\chi^2 = 63.01$		$p < 0.001$	

[a] The row percentages indicate the percentage distribution of the symptoms and signs of the neuropathic and normal subjects for each subgroup, and the column percentages indicate the percentage distribution of the cases of neuropathy and normality for the symptoms and signs.
[b] There was a significantly higher prevalence of neuropathy for subjects with symptoms and signs versus subjects with no symptoms and signs in each subgroup.

neuropathy was observed among subjects who showed indicators of heavy exposure to dioxin (12 out of 55, 22 %). This prevalence was almost three times greater than that of subjects who did not show these indicators. The high frequency of neuropathy found for subjects with chloracne is interesting because chloracne is a good indicator of exposure to dioxin. Moreover, during the monitoring, chloracne was found only in the young age group (0 to 20 a) (8), for which the frequency of neuropathic signs was very low. In fact, the PRR of neuropathy for the subjects under 20 a of age with chloracne versus those without it reached 4.7 (95 % CL, 1.2—18.1), a value greater than the one (2.6) observed in the chloracne subjects of all ages. In contrast, since abnormal hepatic enzyme levels were more common in the adult age group, their association with peripheral neuropathy may not be so unusual.

It must be stressed that no acute polyneuropathy was found during the study, and the polyneuropathic cases found were not severe. The electrophysiological diagnosis of peripheral neuropathy was considered the most appropriate procedure with which to study the possible chronic effects of dioxin-TCDD exposure on the peripheral nerves of a general population.

At the follow-up examination the rate of nonattendants was high, about 56 %. An analysis was carried out to determine whether the group of 277 subjects reexamined in 1978 was positively self-selected as regards the disease under study because of the presence of symptoms and clinical signs which could have encouraged the affected subjects to come to the clinic or because of the presence of factors predisposing towards peripheral neuropathy. The frequency of these possible neuropathy-related factors was not significantly higher among those reexamined with respect to those not reexamined. Moreover, more subjects with chloracne and abnormal serum hepatic enzyme levels were not reexamined in the second screening. The hypothesis that subjects who returned were positively self-selected with respect to the disease under study was not therefore confirmed by this analysis. The coexistent neuropathy and chloracne among subjects exposed to dioxin may represent an important qualitative finding for the identification of subjects at risk.

A neurological follow-up of this population is in progress. The principal objectives are to increase the examination attendance to at least 95 % and to improve the information on the "exposure indicators."

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