ENVIRONMENTAL RESEARCH 27, 457–465 (1982)

Neurological Abnormalities in Chronic Benzene Poisoning. A Study of Six Patients with Aplastic Anemia and Two with Preleukemia[1]

AYNUR BASLO AND MUZAFFER AKSOY

The Section of Hematology of Internal Clinic and Department of Neurology of Istanbul Medical School, Çapa, Istanbul

Received November 18, 1978

Neurological, electromyographical and motor conduction velocity examinations were applied to 6 patients with aplastic anemia and two cases of preleukemia due to chronic exposure to benzene. In addition, sensory conduction velocities were measured in three patients. Neurological abnormalities were found in four out of six pancytopenic individuals. There was a certain relationship between the presence of neurological abnormalities and the period of cessation of the exposure. In the two patients with preleukemia similar neurologic abnormalities were found.

INTRODUCTION

The effects of chronic benzene poisoning on hematopoietic tissue are well known. However, although in his reports on benzene Truhaut (1967, 1968) has indicated the possibility of long-term effects of this chemical agent on the nervous system, such as polyneuritis of the lower extremities, there are very few detailed studies showing the exact deleterious effect of chronic benzene poisoning on the nervous system.

In the last few years we have performed a neurological study in eight cases of chronic benzene poisoning. Six of them showed the findings of aplastic anemia and the other two manifested those of preleukemia. The purpose of this paper is to report the results of this study.

CASE MATERIAL AND METHODS

The series consisted of seven males and one female ranging from 19 to 51 years of age with an average of 35.3 years. Six patients were shoemakers in small shops. One patient (case 3) manufactured objects made of leather. The benzene content of the adhesives used ranged between 9 and 88% with a mean of 50% as determined by gas chromatography in the laboratory of the Turkish Department of Labor (İŞGÜM), Ankara (1972). Another patient (case 6) was engaged in a job manufacturing whistles. For this purpose she dipped plastic material into an open vessel of benzene solution, containing 88.42% benzene and 9.25% toluene determined by gas chromatography. The concentration of benzene in their working environments, measured by a Dräger–Spürgerat MultiGas Detector, Model 21

[1] This study was supported by a grant from TÜBİTAK, the Unit "Hemolytic Anemias and Chemical Hematotoxic Disorders."

0013-9351/82/020457-09$02.00/0

(Lübeck) was recorded to reach 210 or more when benzene-containing adhesives were used.

The hematological methods were all standard procedures and are described elsewhere (Aksoy *et al.*, 1972). Neurological, electromyographical, and motor conduction velocity examinations were applied in the cases studied. In addition, sensory conduction velocities were measured in three patients (cases 1, 5, and 6). In one patient (case 8) electromyographic (EMG) examination could not be applied, but conduction velocity was measured. For EMG examination a DISA (Denmark) type 14a30 three-channel electromyograph with a 13 K 05 concentric needle electrode was used. Action potentials were visualized on a type 14B70 display monitor. A ratio of polyphasic motor unit potential (PMUP) to normal potentials was over 2/10 and was considered as an increased level. In each case at least three muscles, extensor digitorum brevis, tibialis anterior, and gastrocnemius (EDB, TA, GC), were examined during rest, mild, and maximal contractions. Increased ratio of PMUP and insufficient interference patterns were accepted as neurogenic involvement and, moreover, fibrillation and/or sharp waves as denervation. 13 K 62 surface electrodes and concentric needles were used to record motor conduction velocity measurements. During sensory conduction velocity, Teflon-coated needle electrodes were used for recording and 13 K 69 electrodes for stimulation (Buchthal and Rosenfalck, 1965; Di Benedetke, 1970).

RESULTS

Clinical and Hematological Features

Some clinical, hematological, and bone marrow findings are given in Table 1. Six patients had anemia due to chronic exposure to benzene. The period of exposure varied from 6 months to 8 years with a mean of 6 years. They all had a severe or moderate pancytopenia. Bone marrow was hypocellular in four cases and normocellular in one. In one patient (case 1) bone marrow puncture was performed in another hospital and, according to the statement of the attending physician, the findings were consistent with the diagnosis of aplastic anemia. Duration of nonexposure, namely, the period between the cessation of exposure and the performance of neurological examinations, varied between 1 and 96 months. Four patients recovered completely. Two died from bone marrow depression (cases 3 and 4). Two patients (cases 7 and 8) had preleukemia due to chronic exposure to benzene. These patients are described elsewhere (Aksoy *et al.*, 1974). The criteria for the diagnosis of preleukemia were similar to those of Wintrobe *et al.* (1974). One of the patients (case 8) had in addition to preleukemia, α or β-thalassemia with normal levels of hemoglobins A_2 and F.

Results of Neurological Examinations

In one patient (case 1) sensory vibration was decreased and there was a global atrophy of the right leg. In three patients (cases 2, 3, and 8) deep reflexes of both sides were exaggerated and in one (case 8) distal superficial sensory disturbance was detected on upper extremities, while other cases were normal.

TABLE 1

SOME CLINICAL, HEMATOLOGICAL, AND BONE MARROW FINDINGS IN SIX PATIENTS WITH APLASTIC ANEMIA AND IN TWO WITH PRELEUKEMIA

TABLE 1

SOME CLINICAL, HEMATOLOGICAL, AND BONE MARROW FINDINGS IN SIX PATIENTS WITH APLASTIC ANEMIA AND IN TWO WITH PRELEUKEMIA DUE TO CHRONIC BENZENE POISONING

	1	2	3	4	5	6	7	8
Age (years)	19	29	51	42	20	32	42	48
Duration of symptoms (months)	12	2	61	8	6	1	12	10
Duration of exposure (years)	7	6	8	6	8	½	15	10
Duration of nonexposure (months)	6	1	53	96	4	5	8	6
Occupation	Shoem.	Shoem.	Leather worker	Shoem.	Shoem.	Whistle maker	Shoem.	Shoem.
Outcome	CR	CR	F	F	CR	CR	F	F
Diagnosis	Ap. an.	Ap. an.	Ap. an.	Ap. an.	Ap. an.	Ap. an.	Prel.	Prel.
RBC (10^6/mm^3)	3.20	3.15	1.70	2.05	1.45	2.12	1.46	3.00
Hb (g%)	8.3	9.4	4	6.4	5.6	5.6	3.2	6.3
WBC (mm^{-3})	3300	2800	3200	2800	3600	1200	2600	6400
Platelets (10^3/mm^3)	140	102	29	37	10	47	30	140
Hematocrit (%)	30	30	16	18	14	19	11	23
MCV (μ^3)	93	95	94	90	96	90	76	76
Myeloblasts (%)	0	0	0	0	0	0	15	3
Lymphocytes (%)	26	26	59	58	71	52	36	45
NRC (per 100 WBC)	0	0	0	0	0	0	10	0
Fetal hemoglobin (%)	8.3	5.0	19.5		13.6	5.5	40	0
				Bone marrow findings				
Cellularity	Normo.	Hypo.	Hypo.	Hypo.	Hypo.	Hypo.	Hyper.	Hyper.
Myeloblasts (%)		2	1	4	0	0	3	0
Megaloblasts (%)		0	0	1	0	0	2	0
Lymphocytes (%)		12	26	44	21	12	11	8
Myeloid series (%)		42	48	39	51	58	52	16.5
Erythroid series (%)		30	22	9	26	30	35	73

Note. Shoem. = Shoemaker; ap. an. = aplastic anemia; prel. = preleukemia; normo. = normocellular; hypo. = hypocellular. CR = recovered; F = fatal.

Results of EMG and Conduction Velocities (Motor and Sensory)

The results of EMG and motor conduction velocity (MCV) are given in Table 2. The results of sensory velocities of lower and upper extremities are summarized in Tables 3 and 4. In case 1, three EMG examinations were performed during his illness (Fig. 1). He showed global atrophy and decreased sensory vibration of lower extremities. While his aplastic anemia improved, the EMG neurogenic involvement with denervation showed regression at the same time MCV values increased (Table 2). This case was exposed to the toxic substance for 7 years, excepting the last few months. Sensory conduction velocity of the peroneal nerve was normal when it recovered (Table 3). In this patient global atrophy and decreased MCV suggested the presence of neurogenic involvement due to anterior horn and/or peripheral nerve lesions. In case 2, EMG revealed a neurogenic involvement and MCV of peroneal and tibial nerves were normal (Table 2), but MCV of the median nerve showed distal latency lengthening (Table 4). In this case slight distal neurogenic involvement of upper limbs was detected. The patient had been exposed to benzene for 6 years before the performance of neurological examination. Case 3 showed normal EMG and MCV of the peroneal nerve (Table 2), but MCVs of median and ulnar nerves showed distal latency lengthening (Table 4). These findings suggested slight distal neuropathy of upper extremities. He was exposed to benzene for 8 years with the exclusion of the last 53 months. Neurologic findings were not severe, since the patient was not exposed to this toxic agent for a long period. In case 4, EMG and MCV of peroneal and tibial nerves were normal (Table 2). This patient had been exposed to benzene for 6 years and the exposure ceased 96 months earlier. These normal results were probably due to the long period of nonexposure. Case 5 showed normal EMG and normal MCV of peroneal, tibial, median, and ulnar nerves (Tables 2 and 4). In addition, sensory conduction velocity of the median nerve was also normal. This patient was exposed to the toxic agent for 8 years, excepting the last 4 months. In this case it is difficult to explain these normal results. They could be attributed to less exposure to benzene rather than to the short period of nonexposure. Moreover, this patient recovered hematologically in a short period. In case 6, the results of EMG examination and motor conduction studies were normal. But a decrease in the sensory conduction velocities of the lower extremities was observed. In particular, the amplitudes of nerve action potentials were low. Briefly four out of six cases of aplastic anemia showed neurologic abnormalities, but two were normal. These findings suggested that benzene may show toxic effects on the nervous system at the level of peripheral nerve and/or spinal cord.

Preleukemia

In case 7, EMG examination was normal but MCV of the peroneal nerve was decreased (Table 2). MCV of the median nerve showed distal lengthening (Table 4) and sensory conduction velocity (SCV) of the same nerve was decreased. This patient was exposed to benzene for 15 years, excepting the last 8 months. Case 8 has not accepted EMG examination. For that reason, EMG examination and MCV of peroneal and tibial nerves could not be applied. Only MCV of the median nerve was measured and distal latency lengthening was detected (Table 4). This

TABLE 2
THE RESULTS OF ELECTROMYOGRAPHIC AND MOTOR CONDUCTION VELOCITY STUDIES IN SIX PATIENTS WITH APLASTIC ANEMIA AND IN TWO WITH PRELEUKEMIA DUE TO CHRONIC EXPOSURE TO BENZENE

Case No.	Electromyography	Motor conduction velocity	
		N. peronealis (m/sec)	N. tibialis (m/sec)
1	First study: Neurogenic involvement	42.5	51.5
	Second study: Neurogenic involvement and denervation	44	52
	Third study: Regression in mentioned findings	56	52
2	Neurogenic involvement	54	45
3	Normal	64	×
4	Normal	50	40
5	Normal	64	53
6	Normal	56	×
7	Normal	42	40
8	×	×	×

Note. × = Not performed.

patient was exposed to benzene for 10 years and during the last 6 months he has avoided it. In two patients with preleukemia, conduction disturbance was also detected. Because the outcome was fatal, it is difficult to explain this abnormality by a direct effect of benzene. It might be due to a toxic effect of leukemia.

COMMENT

It is generally accepted that in aplastic anemia changes in the nervous system are found only when hemorrhage occurs there (Wintrobe *et al.*, 1974). As can be seen from Tables 2 through 4, neurological abnormalities were found in four out of six pancytopenic individuals with chronic exposure to benzene. This cannot be attributed to the presence of aplastic anemia. Although the clinical and hematological findings of bone marrow depression were of severe or moderate degree in two individuals (cases 3 and 4), they had either no or minimal neurologic abnormalities. Interestingly, in these two patients with aplastic anemia a long period between the cessation of benzene exposure and the performance of neurologic studies, 53 and 96 months, respectively, has been noted. Contrary to this, the above-mentioned period was very short, 1.5 and 6 months, in three pancytopenic individuals associated with changes in the nervous system. On the other hand, in one pancytopenic individual (case 4) without neurological abnormalities the period of nonexposure was as short as 4 months. The absence of changes in nervous system in this patient can possibly be attributed to the lower amount of benzene involved in the period of exposure or to individual susceptibility. On the other hand, although in one patient (case 6) with mild neurological

TABLE 3

THE RESULTS OF THE STUDY ON THE SENSORY CONDUCTION VELOCITIES IN THREE PATIENTS WITH APLASTIC ANEMIA DUE TO CHRONIC BENZENE POISONING

Case No.	Mixed afferent conduction velocity[a]			Pure sensory conduction velocity				
	Conduction time (msec)	Amplitude of NAP (μV)	Conduction velocity (m/sec)	Conduction time[b] (msec)	Amplitude of NAP[b] (μV)	Conduction velocity[b] (m/sec)	Conduction time[c] (msec)	Amplitude of NAP[c] (μV)	Conduction velocity[c] (m/sec)
1	5	10	56	5	6	40	3.3	24	58
5	5	14	54	3.5	10	48.5	3	45	53
6	6.7	4	37	5.5	10	35	4	10	35

Note. NAP = Nerve action potential.

[a] Stimulation: ankle. Recording: collum fibula.

[b] Stimulation: cruris. Recording: dorsum pedis.

[c] Stimulation: cruris. Recording: collum fibula.

TABLE 4
THE RESULTS OF THE STUDIES ON MOTOR CONDUCTION VELOCITIES OF N. MEDIANUS AND ULNARIS IN FOUR PATIENTS WITH APLASTIC ANEMIA AND IN TWO WITH PRELEUKEMIA DUE TO CHRONIC BENZENE POISONING

	N. medianus			N. ulnaris		
		Conduction velocity			Conduction velocity	
Case No.	Distal latency to muscle (msec)	Elbow to wrist (m/sec)	Axilla to elbow (m/sec)	Distal latency to muscle (msec)	Elbow to wrist (m/sec)	Axilla to elbow (m/sec)
2	5.8	55	56	3.8	66	50
3	5.8	64.5	76.5	4.8	55	56
5	4.5	73	62	3.8	71	56
6	5.2	52.5	68	×	×	×
7	5.6	50	63.5	×	×	×
8	5	48	85	×	×	×

Note. × = Not performed.

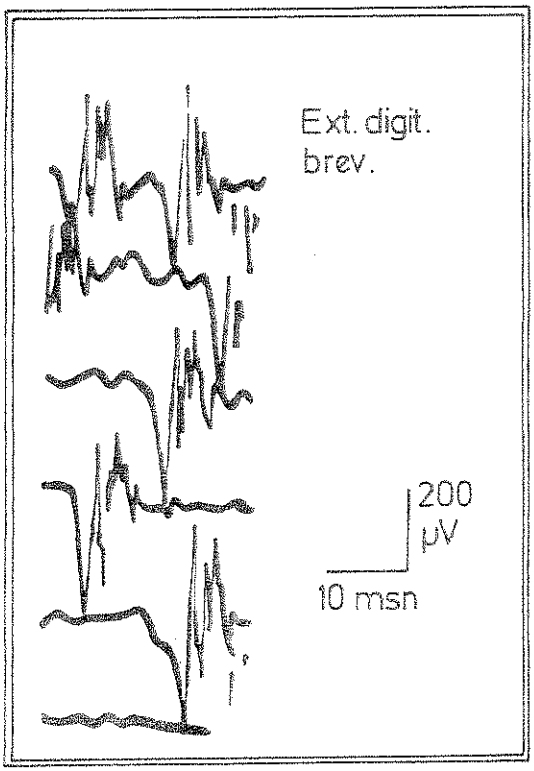

FIG. 1. EMG in case 1, showing polyphasic motor unit potentials.

abnormalities the period of exposure was as short as 6 months, during this period she was exposed very heavily to benzene.

Polyneuritis to *n*-hexane is well established by the studies of Ikeda (1976) and Herskowitz *et al.*, (1971). The absence of this industrial compound in the adhesives and benzene solution used eliminates the possibility of *n*-hexane polyneuritis in our patients. On the other hand, similar changes in the nervous system were observed by an experimental study performed by Matsumato (1971) on chronic toluene poisoning in rats. Electric threshold velocities (motor nerves) were measured after chronic exposure to toluene. An increase was noted in the ratio of threshold stimuli and a decrease in the maximal conduction velocity. These changes were attributed to the influence of toluene on the nervous system. Contrary to *n*-hexane, the role of toluene in the development of neurological abnormalities observed in our patients cannot be eliminated easily because of possible presence of toluene in adhesives or in the solution used by our patients, although at a low level ranging between 6.37 and 9.25%.

Kahn and Muzyka (1973) have observed that in 74 workers with benzene exposure there were complaints indicating functional derangements in the activities of the central nervous system, although hematological abnormalities which are characteristic of benzene poisoning were usually not seen. Many of the workers examined had increased δ-aminolevulinic acid in erythrocytes and some increased coproporphyrin in urine. On the other hand, they experimentally showed that chronic benzene intoxication has some effects on the porphyrin metabolism in rabbits. In this study they have found that benzene poisoning causes changes in the levels of δ-aminolevulinic acid, porphobilinogen, and coproporphyrin in the central nervous system. In spite of these clinical and experimental findings they did not study the peripheral nervous system. But porphyrinic polyneuropathy is a well-known entity and in our opinion this metabolic derangement may cause polyneuropathy in patients who were exposed to benzene.

In view of the above mentioned facts we are strongly inclined to suggest that the neurological abnormalities found in these four pancytopenic individuals are due to the direct effect of benzene or toluene on peripheral nerves and/or the spinal cord. This problem needs investigation, particularly using animal experiments.

REFERENCES

Aksoy, M., Dinçol, K., Akgün, T., Erdem, Ş., and Dinçol, G. (1971). Haematological effects of chronic benzene poisoning in 217 workers. *Brit. J. Ind. Med.* **28**, 296–302.

Aksoy, M., Dinçol, K., Erdem, Ş., Akgün, T., and Dinçol, G. (1972). Details of blood changes in 32 patients with pancytopenia associated with long-term exposure to benzene. *Brit. J. Ind. Med.* **29**, 56–63.

Aksoy, M., Erdem, Ş., and Dinçol, G. (1974). Leukemia in shoe-workers exposed chronically to benzene. *Blood* **44**, 837–841.

Buchthal, F, and Rosenfalck, A. (1965). Action potentials from sensory nerve in man. *Acta Neurol. Scand.* **41**, Suppl. 13, 263–266.

Di Benedetke, M. (1970). Sensory nerve conduction in lower extremities. *Arch. Phys. Med.* **51**, 233–258.

Herskowitz, A., Ishii, N., and Schaumberg, H. (1971). *N*-hexane neuropathy. A syndrome occurring as a result of industrial exposure. *N. Engl. J. Med.* **285**, 82–85.

Ikeda, M. (1976). Poisoning due to benzene and its substitutes in Japan. Report. *In* "Proceedings, International Workshop of Toxicology of Benzene. Paris, 9–11 November" pp. 1–11.

Kahn, H., and Muzyka, V. (1973). The chronic effect of benzene on porphyrin metabolism. *Work Environm. Health* 10, 140–143.

Matsumato, T. (1971). Experimental studies on the chronic toluene poisoning. 2. Electrophysiological changes of neuromuscular function in the rats exposed to toluene. *Ind. Med.* 13, 399–407.

Mayer, R. F. (1963). Nerve conduction studies in man. *Neurology* 13, 1021–1030.

Truhaut, R. (1967). The replacement of benzene by less toxic solvents. *In* "Proceedings, Meeting of Experts on the Safe Use of Benzene and Solvents Containing Benzene, Geneva, 16–22 May 1967," pp. 1–36. International Labor Office, Geneva.

Truhaut, R. (1968). "As Rapporteur of the Report of the Meeting of Experts on the Safe Use of Benzene and Solvents Containing Benzene (1968). Benzene: Uses, Toxic Effects, Substitutes," pp. 1–24. International Labor Office, Geneva.

Wintrobe, M. M., Lee, G. R., Boggs, D. R., Bithell, T. C., Athens, J. W., and Foerster, J. (1974). "Clinical Hematology," Lea & Febiger, Philadelphia.