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EFFECTS OF OCCUPATIONAL EXPOSURE TO ARSENIC ON THE NERVOUS SYSTEM: CLINICAL AND NEUROPHYSIOLOGICAL STUDIES

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Abstract
Objectives: A number of metals, especially heavy metals, exhibit neurotoxic properties. Neurological and neurophysiological studies indicate that the functions of the central (CNS) and peripheral nervous system (PNS) may be impaired under conditions of exposure to arsenic (As). The aim of the present study was to assess the effects of inorganic arsenic on the central and peripheral nervous system. **Materials and Methods:** The study covered a group of 21 male workers (mean age: 41.9 yr; SD: 7.6; range: 31–55 yr) employed in a copper smelting factory. Their employment duration ranged from 5 to 33 years (mean: 18.1 yr; SD: 7.8). Arsenic concentrations in workplace air amounted to 0.01003 mg/m^3 on average (SD: 0.00866). Urine arsenic concentrations ranged from 3.48 to 23.63 μg/l (mean: 11.91 μg/l; SD: 9.5). The control group consisted of 16 males non-occupationally exposed to As, matched for gender, age and work shift pattern. The evaluation of neurological effects was based on the findings of neurological examination, electroencephalography (EEG), visual evoked potentials (VEPs) and electroneurography (ENeG). **Results:** Clinical symptoms, such as sleeplessness or sleepiness, irritability, headache, painful spasms in extremity muscles, extremity paresthesia and pain, and muscular fatigue prevailed among functional disorders of the nervous system in workers chronically exposed to As. Neurological examination did not reveal any organic lesions in the CNS or PNS. In EEG records classified as abnormal, generalized changes were most common. VEP examinations revealed abnormalities in evoked response latency. Stimulation of the motor fibers of the peroneal and medial nerves resulted in a decreased amplitude of the motor potential. Stimulation of the sensory fibers of medial nerves brought about a decreased amplitude of the sensory potential and a lower conduction velocity of the sural nerves. **Conclusion:** The findings of the study indicate that exposure to As concentrations within the threshold limit values (TLV) can induce subclinical effects on the nervous system, especially subclinical neuropathy.

Key words:
Arsenic, Occupational exposure, Nervous system, Neurophysiological findings

INTRODUCTION

Clinical observations and epidemiological studies provide evidence that a long-term exposure to arsenic (As) and its inorganic compounds (i-As) produces adverse effects on numerous body organs and systems [1]. Changes within the respiratory, cardiovascular, hemopoietic, central and peripheral nervous systems, as well as skin and liver lesions and damage to the optic, auditory and olfactory nerves have been well documented in literature [2]. Carcinogenicity and neurotoxicity are the major effects of occupational exposure to As and its inorganic compounds [3,4]. Under conditions of occupational exposure, the effects on the central nervous system (CNS) manifested as cognitive and behavioral disorders, concentration difficulties or autism, are rather sparse [5,6], whereas the peripheral nervous system (PNS) is a critical target. Arsenic-induced

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polyneuropathy is characterized by significantly more intense sensory disorders in the form of paresthesia, painful spasms and hyperesthesia. The symptoms are usually symmetric and long-lasting [7,8]. In the work environment, copper smelting factories are the major source of arsenic exposure [9,10]. Feldman et al. [11] described the symptoms of clinical and subclinical polyneuropathies in smelter workers presenting with high urine As concentrations (250 μg/l). Clinical investigations, including electroneurographic (ENeG) testing of the peripheral nerves showed signs of distal axonopathy. In the 1980s, similar studies on persons exposed to As concentrations changing over time from 500 to 50 μg/m^3 were performed by Swedish researchers who reported neurological symptoms and conduction velocity disorders in the peripheral nerves [12,13].

The aim of this study was to identify the effects of occupational exposure to arsenic and its inorganic compounds on the nervous system under conditions of exposure within the OEL values**.** To this end, neurological and neurophysiological methods were applied.

MATERIALS AND METHODS

Study population

Neurological examinations were conducted under ambulatory conditions in a group of 21 male workers, aged 31–55 years (mean: 41.9 yr; SD: 7.6), employed at different workposts (refiners, copper electrolyzers and crane operators) in a copper smelter (Table 1). Exposure duration ranged from 5 to 33 years (mean: 18.1 yr; SD: 7.6). The workers were exposed to low As concentrations. The control group was composed of 16 males (mean age: 46.1 yr; SD: 9.5) free from exposure to chemical agents, who were matched for gender, age and work shift pattern.

Table 1. Study and control populations by age

Group	N	Age (years)			
		min	max	$\bar{x}$	SD
Study	21	31	55	41.90	7.6
Control	16	27	57	46.06	9.5
F = 2.168	p = 0.15 ns	–	–	–	–
Total	37	27	57	43.70	8.6

SD — standard deviation; ns — non-significant.

The exclusion criteria were as follows: suspected or past disorders of the nervous system, such as craniocerebral traumas, cerebrovascular disease, neuroinfections, brain tumors, migraine, diabetes, arterial hypertension, suspected alcohol addiction, symptoms of nicotine addiction, abuse of medicines with a known impact on electroencephalography (EEG) and visual evoked potentials (VEPs), as well as spondylosis with a radicular syndrome, and visual disorders.

Neurological and neurophysiological examinations

Clinical neurological examinations were performed in all the subjects from the control and study groups according to the study protocol and commonly adopted methodology. Electroencephalography (EEG) was recorded using Digital EEG Pegasus units with the international system of 10–20 electrodes and activation involving hyperventilation and photostimulation. The obtained results were classified as normal, borderline or abnormal [14].

Visual evoked potentials were recorded using Dantec 2000C Neuromatic unit (Dantec, Denmark). We used monocular full field checkerboard stimulation, with the frequency of pattern reversal of 2 Hz and the mean luminance of TV monitor of 20 cd/m^3 Biological activity was recorded from the montage of O_z to F_z and sweep duration of 300 ms. A total of 2×200 individual responses was averaged.

The averaged latency of N1, P100 and N2, N1P100 components and P100 N2 amplitudes and the configuration of visual evoked response (VER) were assessed.

The Dantec 2000C Neuromatic unit (Dantec, Denmark) was also used to perform ENeG testing. To assess the function of the peripheral nerves, motor and sensory fibers (peroneal, sural and medial) were stimulated in each patient, using commonly adopted techniques [15]. Conduction velocity, distal motor latency, response amplitude, and nerve sensory potential amplitude were determined. Stimulation was performed using surface electrodes, types 13K60 and 13L36 (Dantec, Denmark).

Exposure assessment

Occupational exposure of workers was assessed by determining As concentrations in urine and workplace air. Individual air sampling in the workers' breathing zone was applied (Casell-AFC-123; flow rate: 2 l/min). The concentration of As in workplace air, which was measured using individual dosimetry, ranged from 0.0037 to 0.03022 mg/m^3 ($\bar{x}$ = 0.01003 mg/m^3; SD: 0.00866). In the study group, an increase in As concentrations in workplace air: threefold (0.03022 mg/m^3) and twofold (0.0273 mg/m^3), was found at workposts of two workers.

Total arsenic concentrations in urine samples collected after the work shifts were determined using inductively coupled plasma mass spectrometer (ICP-MS) (Agilent 7500 ce, Agilent Technologies, Waldbronn, Germany). In the study group, urine As concentrations ranged from 3.48 to 23.63 μg/l (SD: 9.5).

Statistical analysis

The results were analyzed using the F-Fisher test, Fisher exact test and Pearson correlation coefficient.

RESULTS

Neurological and neurophysiological findings

The most frequent CNS-related complaints reported by the workers exposed to arsenic included sleeplessness or sleepiness, irritability and headaches. Among these complaints, sleeplessness, manifested by difficulties in falling asleep, awakening at night and waking early in the morning, was reported most frequently (p = 0.037); however, the respondents did not relate these symptoms to the shift work pattern.

Peripheral nervous system symptoms were described by the exposed workers as painful spasms in extremity muscles (28.0%) usually occurring at night; pain (19.0%) and extremity paresthesia (14.3%), manifested as the fornication and numbness, mostly in the distal segments. The subjects stressed that the symptoms tended to be worse at night.

Muscular fatigue, mainly in lower extremities, was the predominant symptom (47.6%). It was significantly more prevalent (p = 0.001) among the workers who did not link it with their body posture at work.

Table 2 shows the results of Pearson correlation analysis for the relationship between neurological effects and exposure duration or As concentration in urine or workplace air. Statistically significant (p = 0.05) relationship was observed between the duration of exposure and the reported extremity paresthesia (0.62). The relationship between urine As concentration and sleepiness was moderate (–0.38). The remaining relationships were weak and statistically non-significant.

The neurological examination of the exposed workers did not reveal any symptoms of organic lesions of the central or peripheral nervous system that would result from occupational exposure. There were no grounds for the clinical diagnosis of encephalopathy or polyneuropathy related to the working conditions.

In the study group, 57.1% of EEG records were assessed as normal; 4.8% as borderline; and 38.1% as abnormal (Table 3). In the control group, normal EEG records were found in 62.5%; borderline in 12.5% and abnormal in 25.0% of the subjects. The comparison of EEG records between the study and control group did not show statistically significant differences.

Table 2. Relationship between neurological symptoms in the study group (N = 21) and exposure duration (years) or As concentration in urine or workplace air (based on Pearson correlation coefficient)

Symptoms	Exposure duration (years)	As concentration in urine	As concentration in workplace air
Headache	–0.070	–0.134	–0.102
Irritability	0.150	0.066	–0.155
Sleeplessness	0.099	–0.114	–0.242
Sleepiness	–0.260	–0.378	–0.162
Spasms in extremity muscles	–0.049	–0.042	–0.142
Muscular fatigue	–0.024	0.008	0.233
Extremity pains	0.105	0.033	–0.115
Paresthesia	0.619*	0.136	–0.103

* Significant at p = 0.05.

Table 3. The rate of EEG changes in the study and control group

Group	Normal EEG n (%)			Abnormal EEG n (%)			
	normal	borderline	abnormal	generalized	focal	paroxysmal	asymmetric
Study (N = 21)	12 (57.1)	1 (4.8)	8 (38.1)	3 (37.5)	2 (25)	2 (25)	1 (12.5)
Control (N = 16)	10 (62.5)	2 (12.5)	4 (25.0)	2 (50.0)	1 (25)	1 (25)	0
Fisher exact test	ns	ns	ns	ns	ns	ns	ns

ns — non-significant.

In the study group, EEG findings that showed generalized changes prevailed among the abnormal records (37.5%). They were characterized by irregular background activity: the loss and deformation of alpha background rhythm, the presence of slow theta waves of varying frequency (4–7 Hz) and the amplitude of usually up to 40–59 μV, occurring in all leads. Focal changes, located mainly in the right temporal leads, were found in two (25.0%) subjects. Paroxysmal EEG changes assumed the form of generalized slow dysrhythmic theta wave discharges (4–7 Hz) and single sharp waves lasting 80–200 ms, both of which occurred against the unchanged background activity. EEG records classified as asymmetric (dominant alpha rhythm) were registered in one subject (12.5%).

The analysis of abnormal EEG records showed that the longer the occupational exposure, the more frequent the changes in EEG records (r = 0.53, statistically significant at p = 0.01). However, no relationship was found between As concentrations in urine or workplace air and abnormal EEG findings[1].

Borderline records were found in one person (4.8%). The classification criteria for this type were the presence of one normal background rhythm, usually alpha rhythm, and of slow theta waves in 5–15% of the records.

The analysis of visual evoked potentials showed a significantly prolonged monocular potential latency of the P100 component as compared with the finding for the control group (p = 0.01) (Table 4).

[1] Since it was impossible for the authors to present all the statistical calculations conducted during the study, the data are not published. However, the authors can make them available on request.

Table 4. Latency and amplitude of visual evoked potentials (VEPs) in the study and control group

Group	VEPs latency (ms)						VEPs amplitude (μV)			
	RE stimulation			LE stimulation			RE stimulation		LE stimulation	
	N1	P100	N2	N1	P100	N2	N1P100	P100N2	N1P100	P100N2
Study (N = 21)										
$\bar{x}$	76.40	100.1	124.5	77.30	101.20	124.4	6.2	5.9	5.4	5.7
SD	6.80	5.6	11.0	7.00	5.00	10.5	3.1	2.8	2.7	3.1
Control (N = 16)										
$\bar{x}$	71.10	97.2	122.4	68.00	96.20	125.0	6.9	7.2	6.7	7.6
SD	4.10	5.4	12.3	5.20	5.70	10.3	3.1	2.6	2.8	2.9
Fisher test	0.01**	ns	ns	0.001***	0.008**	ns	ns	ns	ns	ns

RE — right eye, LE — left eye.
SD — standard deviation; ns — non-significant.
* Significant at p = 0.05.
** Significant at p = 0.01.
*** Significant at p = 0.001.

Table 5. Relationship between visual evoked potentials (VEPs) in the study group (N = 21) and exposure duration (years) or As concentration in urine or workplace air (based on Pearson correlation coefficient)

Parameter	Exposure duration (years)	As concentration in urine	As concentration in workplace air
Latency N1 RE	–0.079	–0.117	–0.097
Latency P100 RE	–0.199	0.229	0.008
Latency N2 RE	–0.246	–0.038	0.014
Latency N1 LE	–0.127	–0.202	0.286
Latency P100 LE	–0.399	–0.120	–0.141
Latency N2 LE	–0.126	–0.185	–0.039
Amplitude N1P100 RE	–0.026	0.233	–0.289
Amplitude P100N2 RE	0.389	0.031	–0.297
Amplitude N1P100 LE	0.099	0.362	–0.124
Amplitude P100N2 LE	0.398	0.098	–0.217

RE — right eye, LE — left eye.

The comparison of the main P100 component amplitudes between the study and control group showed lower values among the exposed workers; however, the differences were not statistically significant.

Pearson correlation coefficient revealed no statistically significant relationship between VEP parameters and exposure duration or between VEP and As concentration in urine or workplace air (Table 5). However, a moderate relationship was found between P100 latency after left eye stimulation (–0.40), P100N2 amplitude for right eye (0.40) and P100N2 amplitude for left eye (0.40). Furthermore, a moderate relationship was observed between As concentration in urine and N1P100 amplitude for left eye (0.36).

The results of electroneurographic examination are summarized in Tables 6 and 7. Statistically significant

Table 6. Electroneurographic (ENeG) findings in the study and control group

Group	Motor fiber stimulation								
	medial nerve			peroneal nerves					
				right			left		
	Conduction velocity (m/s)	Response amplitude (mV)	Standardized distal latency (ms/cm)	Conduction velocity (m/s)	Response amplitude (mV)	Standardized distal latency (ms/cm)	Conduction velocity (m/s)	Response amplitude (mV)	Standardized distal latency (ms/cm)
Study (N = 21)									
$\bar{x}$	57.0	11.10	0.57	51.0	12.00	0.59	49.20	12.70	0.58
SD	5.2	5.30	0.06	6.7	6.20	0.10	6.00	6.00	0.10
Control (N = 16)									
$\bar{x}$	58.1	17.80	0.58	54.3	16.80	0.58	53.50	17.40	0.59
SD	7.6	2.50	0.05	4.8	2.90	0.05	4.70	3.00	0.06
Fisher test	ns	0.001***	ns	ns	0.008**	ns	0.026*	0.007**	ns

SD — standard deviation; ns — non-significant.
* Significant at p = 0.05.
** Significant at p = 0.01.
*** Significant at p = 0.001.

Table 7. Electroneurographic (ENeG) findings in the study and control group

Group	Sensory fiber stimulation			
	medial nerve		sural nerve	
	conduction velocity (m/s)	sensory potential amplitude (μV)	conduction velocity (m/s)	sensory potential amplitude (μV)
Study (N = 21)				
$\bar{x}$	59.2	9.06	54.60	15.56
SD	10.4	4.26	6.70	7.07
Control (N = 16)				
$\bar{x}$	59.0	13.77	60.00	17.26
SD	7.0	3.26	5.60	5.37
Fisher test	ns	0.001***	0.015*	ns

SD — standard deviation; ns — non-significant.
* Significant at p = 0.05.
** Significant at p = 0.01.
*** Significant at p = 0.001.

(p = 0.001) reduction in response amplitude, compared with the control group, referred to the medial nerve.

More pronounced differences, relative to the control group, were found in the stimulation of the peroneal nerves. A statistically significant (p = 0.01) decrease in response amplitude for both nerves and a lower motor conduction velocity (MCV) were observed after stimulation of left nerve (p = 0.05).

The changes found in the sensory fibers of the medial nerve were characterized by a statistically significant (p = 0.001) decrease in the amplitude of the nerve sensory potential at normal sensory conduction velocity (SCV).

Table 8. Relationship between motor conduction velocity (MCV) in peripheral nerves in the study group (N = 21) and exposure duration (years) or As concentration in urine or workplace air (based on Pearson correlation coefficient)

Parameter	Exposure duration (years)	As concentration in urine	As concentration in workplace air
Medial nerve			
conduction velocity	–0.443*	–0.261	–0.187
response amplitude	0.021	0.029	–0.121
standardized distal latency	–0.131	0.144	–0.154
Peroneal nerve (right)			
conduction velocity	–0.101	0.128	0.050
response amplitude	–0.106	–0.128	0.130
standardized distal latency	0.092	0.134	–0.195
Peroneal nerve (left)			
conduction velocity	0.325	0.161	–0.053
response amplitude	–0.121	–0.163	0.195
standardized distal latency	0.122	0.144	–0.259

* Significant at p = 0.05.

The sural nerve changes were marked by a significant (p = 0.05) slowing down of SCV and a non-significant decrease in the amplitude of the nerve sensory potential, as compared with the findings for the control group. The analysis using Pearson correlation coefficient revealed no statistically significant relations, except for a moderate relationship between exposure duration and MCV of the medial nerve (–0.44). Relatively indicative, although statistically non-significant, relationships were observed between (a) exposure duration and conduction velocity of

Table 9. Relationship between sensory conduction velocity (SCV) in peripheral nerves in the study group (N = 21) and exposure duration (years) or As concentration in urine or workplace air (based on Pearson correlation coefficient)

Parameter	Exposure duration (years)	As concentration in urine	As concentration in workplace air
Medial nerve			
conduction velocity	0.021	–0.041	–0.103
sensory potential amplitude	–0.024	–0.059	0.272
Sural nerve			
conduction velocity	0.193	–0.039	0.066
sensory potential amplitude	0.069	–0.239	0.454*

* Significant at p = 0.05.

left peroneal nerve (0.33), (b) As concentration in urine and motor nerve conduction velocity of the medial nerve (–0.26) and (c) As concentration in workplace air and distal latency after stimulation of left peroneal nerve (–0.26) (Table 8).

Pearson correlation coefficients proved to be statistically significant with respect to the relationship between As concentrations in workplace air and the amplitude of the sural nerve sensory potential (0.45) (Table 9).

DISCUSSION

In the clinical pattern of impaired nervous system function, which was observed under conditions of exposure to inorganic As (Polish OEL is 0.01 mg/m^3), sleep disturbances and extremity fatigue prevailed. However, headache, irritability, spasms of extremity muscles, and pain and paresthesia of lower extremities were noted as well. Reported most frequently were the complaints pertaining to the peripheral nervous system.

A strong relationship could be observed between extremity paresthesia and exposure duration and a moderate relationship between sleepiness and urine As concentrations. The neurological examination, as an objective method, revealed no symptoms of damage to the central or peripheral nervous system. In particular, the symptoms reported by other authors, such as extremity paresis, reflex disorders, muscular atrophy or sensory disorders, were not detected in our study population [16,17]. The study findings did not provide grounds for the clinical diagnosis of toxic encephalopathy or polyneuropathy. With regard to the neurophysiological examinations, the changes revealed by electroneurography were most pronounced. They were frequently manifested by a decreased response amplitude after stimulation of the motor fibers of the medial and peroneal nerves and a decreased amplitude of the sensory potential of the medial nerve at normal values of conduction velocity.

A slowdown in conduction velocity was observed in the sural nerve as compared with the findings for the control group; however, these values were not significantly different from the laboratory standards. When compared with the control values, the amplitude of the nerve sensory potential was reduced, but not at a significant level, and it did not stand off the laboratory standards. Tseng et al. [18] presume that the slowed down conduction velocity of the sensory nerve and the changes in the amplitude of the sural nerve sensory potential are an early marker of arsenic-induced polyneuropathy.

The abnormalities in the ENeG records, concerning mainly the response amplitudes of relevant peripheral nerves, point to the subclinical symptoms of axonal polyneuropathy. Feldman et al. [11] and Seppäläinen [19] reported similar findings. Blom at al. [12] analyzed the results of the studies performed on a group of smelter workers exposed to As, with airborne As concentrations changing over time from 500 mg/m^3 (until 1975) to 50 mg/m^3 [12]. On ENeG examination, they presented with reduced sensory and motor conduction velocity in the peripheral nerves, which correlated with As exposure parameters. However, the authors did not find a significant relationship between ENeG abnormalities and urine As concentrations.

In the reported studies, indicative but not statistically significant relationships were found between some ENeG parameters and duration of exposure (years) or As concentration in workplace air. This is consistent with the findings of other researchers [20]. Lagerkvist and Zetterland [13] stressed that the duration of As exposure plays a more significant role with respect to the condition of peripheral nerves.

We decided to perform VEP examinations on account of early literature reports on the retrobulbar lesion of the optic nerve as a result of inorganic arsenic poisoning [2]. The VEP findings showed that the latency of particular components fell within laboratory standards.

The changes in N1 and P100 latencies were more frequently observed among the exposed workers. It is worth noting that in the exposed persons, the slightly reduced amplitude of the main P100 component was not statistically significant. None of the workers presented the absence of VEP. Abnormal VEP findings were noted in 9 (42.8%) persons. The study results imply the presence of a dysfunction within the optical neuron. It is rather difficult to

compare our findings with the results of other studies due to the lack of earlier literature reports on this subject.

Reports on EEG examinations in the persons exposed to inorganic arsenic are rather scarce [20]. In early reports, frequent and intensified changes in EEG records were described in children after poisoning with pentavalent inorganic arsenic contained in milk [2]. In our study group, abnormal EEG records made up 38.1%. Generalized changes, usually not much advanced, prevailed (37.5%) among the EEG findings. The incidence of abnormal EEG records was higher in the group of exposed workers, exceeding the so-called "population standard", but it did not significantly differ from that in the control group.

To investigate whether occupational exposure to inorganic As compounds may induce permanent optic nerve disorders or other CNS disorders, it would be necessary to conduct further comprehensive, prospective studies on a more representative population.

CONCLUSIONS

The results of the neurological examinations in our study revealed that occupational exposure to arsenic and its inorganic compounds in a copper smelter, at concentrations within the occupational exposure limits ($\bar{x}$ = 0.01003 mg/m^3 ±0.00866), does not induce organic lesions in the nervous system that would be indicative of toxic encephalopathy or polyneuropathy.

The reported complaints pertaining to the peripheral nervous system and the abnormalities in ENeG records indicate polyneural disorders, such as subclinical polyneuropathies.

Assessment of the conduction velocity in peripheral nerves should be obligatory, especially in the workers who report complaints indicative of a neuropathy.

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