LEAD NEUROTOXICITY

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ABSTRACT

Lead damages the central nervous system, its functions as well as the peripheral nervous system during chronic exposure presenting with non-distinct and asymptomatic aberrations. The mechanisms of neurotoxicity remain not sufficiently clarified yet. The influence of lead on the cognitive process is specified through complex interrelations with depressive symptoms, hypertension, or increased homocysteine levels, which taken alone influence upon the cognitive disorders and enhance the risk of dementia. Blood lead concentrations in which the anomalies in the peripheral nervous system emerge and which structures are predominantly affected are discussed.

Key words: lead neurotoxicity, central nervous system, peripheral nervous system, Alzheimer disease, homocysteine, apolipoprotein E genotype

Despite substantial advances in lead exposure reduction, lead toxicity still remains a significant health problem. Increased usage of lead in the industry increases its dissemination in the environment worldwide. Lead represents a serious health risk not only for the workers but also for the growing up and children. Lead is a cause for permanent health damage of numerous organs and systems at relatively low levels of exposure previously considered safe. Unrecognized health risk in the past is already proved nowadays by the results from the investigations of the chronic exposure at low lead levels in adults and children. Heavy metals and, especially, lead, do not play any physiological role in the biological systems. Lead presence in the human organism is imperceptible, however, it has frequent consequences varying between peripheral neuropathy and cognitive disorders in adults and children. At presence, the rising exposure to lead of adults and children represents the most significant public health problem. The occupational exposure of the workers continues to be an alarming component of this problem. People are in a state of a positive lead balance still after birth onwards.

Lead indirectly influences upon cognitive function either through blood pressure (hypertension), or homocysteine levels. These increased levels are a well-known risk factor for cardiovascular diseases. There is an existing risk for disorders of cognitive functioning and thus of dementia. Homocysteine is a neurotoxin of the central nervous system

as it exerts an effect on the neurotransmitter synthesis and it is related to extracellular death and apoptosis (24). Blood lead concentration determines the homocysteine levels (11,28). Blood lead levels and bone ones are related to blood pressure and hypertension in adults (17,19) and in occupationally exposed population groups (8,9). Hypertension has been identified to be a potential risk factor for dementia (3,13). This is the probable indirect mechanism of lead action in the framework of cognitive disturbances. There is no doubt that fine influences on children's neurophysiological development can be observed even at blood lead levels higher than 20 µg/dL. In a study from the USA there are data about supposed effects at blood lead levels lower than 10 µg/dL (6).

Some authors assume the capacity of lead to modify apolipoprotein E (APOE) genotype and thus to affect cognitive functions (30). The presence of APOE epsilon 4 allele is a risk factor for late-onset Alzheimer disease (18), hippocampal atrophy (20) and senile plaques (34). It seems that APOE epsilon 4 allele decreases the age of onset of the disease and accelerates age-related cognitive disorders. The presence of this genotype is related to the lesions in the nervous tissue (26) and to the reduction of the antioxidant capacities of the organism (33). The interaction of APOE genotype with the lead level in tibia is associated with the disturbed among carriers of APOE epsilon 4 allele to counteract the toxicity of lead exposure.

Fine alterations in the neurophysiological functions have been observed among workers exposed to inorganic lead. These disturbances have been established in terms of visual-motor function, memory, attention and verbal comprehension (12).

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In another study, a subjective improvement of the reduction of the level of stress, anger, depression, fatigue and perplexity as a consequence of a substantial improvement of the occupational exposure and reduction of blood level concentrations, however, without any considerable improvement of the results obtained by means of the fine neurophysiological tests (1). Such effects can be detected in workers with blood lead concentrations of and higher than 50 µg/dL, however, it has been asserted that the sensomotor disturbances of the peripheral nervous system are more sensitive than the cognitive functions and they can be established even at blood lead concentrations lower than 40 µg/dL (32). Nevertheless, there exist other variables, too, which have not been adequately controlled such as alcohol consumption or incidence rate of hypertension and cerebrovascular disease.

According to Goodman et al. (2002), no one of the single investigations can provide convincing evidence when offering information about the subclinical neurobehavioural effects in individuals exposed to lead. Some authors declare that these investigations do not provide sufficient data enabling immediate conclusion about the biological effects of lead at definite levels of exposure (10). Other authors assert that there exists dependence between the blood lead concentrations and the cognitive disorders, worsening the skills and the peripheral sensomotor anomalies observed at lead levels of 18 µg/dL (29).

Another investigation examines the change of the volume of white and gray matter and some other structural brain disturbances which are proved by means of NMR and the cognitive disturbances related to that. Some other disturbances have been revealed, too such as lesions of the architectonics of the brain, reduction of the total volume, *lesions in the area of gyrus cingulate, insula and corpus callosum*, changes of the size of the cells, their architecture, the size and density of synaptic gap. This leads to stable alterations in the brain and progressive diminution of the cognitive functions during the chronic exposure to organic lead compounds and there exists a correlation to the bone lead levels such as those in tibia (31). The chronic occupational exposure to lead causes atrophy and enlarging lesions of the white cerebral matter even years after the cessation of this exposure in a group of workers (27). The total brain volume, the volume of the frontal parts, the total volume of the gray matter and the volume of the parietal white matter are diminished. The measured high bone lead concentrations are associated with the reduced regional volumes of *gyrus cingulate* and *insula* (31). Besides lead damages the auditory nerve distally and the auditory tract in the brainstem. The imperceptible lesions of the hearing have severe consequences, especially for education of the children. Lead affects the *cerebellum* and *vermis* as well (16).

Lead presents with numerous aspects and mechanisms of action when affecting the peripheral nervous system. In addition to the direct action on the nervous or muscular tissues, lead can exert an indirect action on the nerve fibres. Here is an example: lead exposure can cause kidney damage (15) and the diseases of the peripheral nervous system

are associated with chronic renal failure (4). The conductor nerve velocities of the patients who have undergone kidney transplantations are improved (23). An epidemiological study covering the recent years shows that lead can exert a nephrotoxic effect even in blood concentrations below 5 µg/dL (7). Another possible pathogenetic mechanism related to the established liver disorders has been discussed in the literature available. The individuals presenting with acute hepatic porphyria can possess symptoms similar to those of the patients with lead intoxication, including abdominal pain, constipation and motor neuropathy as well as increased production of δ -aminolevulinic acid (5). Besides lead enhances the amount of this acid through inhibition of δ -aminolevulinic acid dehydratase (25). This acid is bound to the receptors of γ -aminobutyric acid (GABA) which represents an inhibitory neurotransmitter in the central nervous system (21).

The peripheral motor neuropathy is considered a result from the chronic high lead exposure level although, as a whole, there is convincing evidence about the reduction of the velocity of the peripheral nerve conductivity even at lower blood lead concentrations.

The results from the study performed by Nora et al. (2000) demonstrate that chronic lead intoxication causes damage of the peripheral nervous system, especially affecting the small non-myelinated fibres (23). Bilinska et al. (2004) establish a significant reduction of some electrophysiological parameters such as amplitude and distal latent time among asymptomatic workers with chronic lead exposure (2). The investigation of the correlation between the blood lead concentrations and electroneurographic parameters demonstrates that the non-myelinated nerve fibres are predominantly affected when this lead concentration is below 33 µg/dL. The disturbances are more outlined in terms of the sensory fibers and the conduction velocities of the motor fibres at preserved amplitudes of the peripheral nerves. They are more manifested in the upper extremities. Lead may reduce the conduction nerve velocities by acting either directly on the peripheral nerves, or indirectly through damage of the kidneys or liver (14).

Various values of blood lead concentrations being the threshold of safety are currently discussed in a series of investigations based on contemporary data about the neurotoxicity. Certain authors comment on the level of 30 µg/dL as a safety level. Nowadays the discussion about the "dose-response" still remains topical.

REFERENCES

1. Baker, E. L., White, R. A., Pothier, L. J., et al. Occupational lead neurotoxicity: improvement in behavioural effects after reduction of exposure. *Br. J. Ind. Med.*, **42**, 1985, 507-516.
2. Bilinska, M., Brzezowska, D., Koszewicz, M., Antonowicz-Juchniewicz, J., Modrzycka, T. Subclinical lead neuropathy. *Pol. Merkur. Lekarski*, **17**, 2004, **99**, 244-247.

3. Birkenhager, W. H., Staessen, J. A. Progress in cardiovascular diseases: cognitive function in essential hypertension. *Prog. Cardiovasc. Dis.*, **49**, 2006, No 1, 1-10.
4. Bolton, C. F. Peripheral neuropathies associated with chronic renal failure. *Can. J. Neurol. Sci.*, **7**, 1980, **2**, 89-96.
5. Bonkowsky, H. L., Schady, W. Neurologic manifestations of acute porphyria. *Semin. Liver Dis.*, **2**, 1982, **2**, 108-124.
6. Cranfield 2003. IPCS Environmental Health Criteria 165: Inorganic Lead 1995; 152-191.
7. Ekong, E. B., Jaar, B. G., Weaver, V. M. Lead-related nephrotoxicity: a review of the epidemiologic evidence. *Kidney Int.*, **70**, 2006, **12**, 2074-2084.
8. Glenn, B. S., Bandeen-Roche, K., Lee, B. K., Weaver, V. M., Todd, A. C., Schwartz, B. S. Changes in systolic blood pressure associated with lead in blood and bone. *Epidemiology*, **17**, 2006, **5**, 538-544.
9. Glenn, B. S., Stewart, W. F., Links, J. M., Todd, A. C., Schwartz, B. S. The longitudinal association of lead with blood pressure. *Epidemiology*, **14**, 2003, **1**, 30-36.
10. Goodman, M., LaVerda, N., Clarke, C., Foster, E. D., Ianuzzi, J., Mandel, J. Neurobehavioural testing in workers occupationally exposed to lead; systematic review and meta-analysis of publications. *Occup. Environ. Med.*, **59**, 2002, 217-223.
11. Guallar, E., Silbergeld, E. K., Navas-Acien, A., Malhotra, S., Astor, B. C., Sharrett, A. R., et al. Confounding of the relation between homocysteine and peripheral arterial disease by lead, cadmium, and renal function. *Am. J. Epidemiol.*, **163**, 2006, **8**, 700-708.
12. Hanninen, H., Aitio, A., Kovala, T., et al. Occupational exposure to lead and neuropsychological dysfunction. *Occup. Environ. Med.*, **55**, 1998, 202-209.
13. Hayden, K. M., Zandi, P. P., Lyketsos, C. G., Khachaturian, A. S., Bastian, L. A., Charoonruk, G., et al. Vascular risk factors for incident Alzheimer disease and vascular dementia: the Cache County study. *Alzheimer Dis. Assoc. Disord.*, **20**, 2006, **2**, 93-100.
14. Krieg, E. F. Jr, Chrislip, D. W., Brightwell, W. S. A meta-analysis of studies investigating the effects of lead exposure on nerve conduction. *Arch. Toxicol.*, **82**, 2008, **8**, 531-542.
15. Loghman-Adham, M. Renal effects of environmental and occupational lead exposure. *Environ. Health Perspect.*, **105**, 1997, **9**, 928-938.
16. Louis, E. D., Applegate, L., Graziano, J. H., Parides, M., Slavkovich, V., Bhat, HK. Interaction between blood lead concentration and delta-amino-levulinic acid dehydratase gene polymorphisms increases the odds of essential tremor. *Mov. Disord.*, **20**, 2005, **9**, 1170-1177.
17. Martin, D., Glass, T. A., Bandeen-Roche, K., Todd, A. C., Shi, W., Schwartz, B. S. Association of blood lead and tibia lead with blood pressure and hypertension in a community sample of older adults. *Am. J. Epidemiol.*, **163**, 2006, **5**, 467-478.
18. Meyer, M. R., Tschanz, J. T., Norton, M. C., Welsh-Bohmer, K. A., Steffens, D. C., Wyse, B. W., et al. APOE genotype predicts when-not whether-one is predisposed to develop Alzheimer disease. *Nat. Genet.*, **19**, 1998, **4**, 321-322.
19. Moffat, S. D., Szekely, C. A., Zonderman, A. B., Kabani, N. J., Resnick, S. M. Longitudinal change in hippocampal volume as a function of apolipoprotein E genotype. *Neurology*, **55**, 2000, **1**, 134-136.
20. Nash, D., Magder, L., Lustberg, M., Sherwin, R. W., Rubin, R. J., Kaufmann, R. B., et al. Blood lead, blood pressure, and hypertension in perimenopausal and postmenopausal women. *JAMA*, **289**, 2003, **12**, 1523-1532.
21. Muller, W. E., Snyder, S. H. D-aminolevulinic acid: influences on synaptic GABA receptor binding may explain CNS symptoms of porphyria. *Ann. Neurol.*, **2**, 1977, **4**, 340-342.
22. Nora, D. B., Gomes, I., Said, G., Carvalho, F. M., Melo, A. Modifications of the sympathetic skin response in workers chronically exposed to lead. *Braz. J. Med. Biol. Res.*, **40**, 2000, **1**, 81-87.
23. Oh, S. J., Clements, R. S. Jr, Lee, Y. W., Diethelm, A. G. Rapid improvement in nerve conduction velocity following renal transplantation. *Ann. Neurol.*, **4**, 1978, **4**, 369-373.
24. Parnetti, L., Bottiglieri, T., Lowenthal, D. Role of homocysteine in age-related vascular and non-vascular diseases. *Aging (Milano)*, **9**, 1997, **4**, 241-257.
25. Piomelli, S. The effects of low-level lead exposure on heme metabolism.- In: Low level lead exposure: the clinical implications of current research. H. L. Needleman, ed. New York, Raven Press, 1980, 67-74.
26. Poirier, J., Sevigny, P. Apolipoprotein E4, cholinergic integrity and the pharmacogenetics of Alzheimer's disease. *J. Neural Transm.*, 1998, Suppl **53**, 199-207.
27. Rowland, A. S., McKinstry, R. C. Lead toxicity, white matter lesions, and aging. *Neurology*, **66**, 2006, **10**, 1464-1465.
28. Schafer, J. H., Glass, T. A., Bressler, J., Todd, A. C., Schwartz, B. S. Blood lead is a predictor of homocysteine levels in a population-based study of older adults. *Environ. Health Perspect.*, **113**, 2005, **1**, 31-35.
29. Schwartz, B. S., Stewart, W., Hu, H. Neurobehavioural testing in workers occupationally exposed to lead. *Occup. Environ. Med.*, **59**, 2002, 648-649.
30. Stewart, W. F., Schwartz, B. S., Simon, D., Kelsey, K., Todd, A. C. ApoE genotype, past adult lead exposure, and neurobehavioral function.- *Environ. Health Perspect.*, **110**, 2002, 501-505.
31. Stewart, W. F., Schwartz, B. S., Davatzikos, C., Shen, D., Liu, D., Wu, X., et al. Past adult lead exposure is linked to neurodegeneration measured by brain MRI. *Neurology*, **66**, 2006, **10**, 1476-1484.
32. Stollery, B. T., Banks, H. A., Broadbent, D. E., Lee, W. R. Cognitive function in lead workers.- *Br. J. Ind. Med.*, **46**, 1989, 698-707.
33. Teter, B., Xu, P. T., Gilbert, J. R., Roses, A. D., Galasko, D., Cole, G. M. Human apolipoprotein E isoform-specific differences in neuronal sprouting in organotypic hippocampal culture. *J. Neurochem.*, **73**, 1999, **6**, 2613-2616.

34. Zubenko, G. S., Stiffler, S., Stabler, S., Kopp, U., Hughes, H. B., Cohen, B. M., et al. Association of the apolipoprotein E epsilon 4 allele with clinical subtypes of autopsy-confirmed Alzheimer's disease. *Am. J. Med. Genet.*, 54, 1994, **3**, 199-205.