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DISORDERS OF IRON METABOLISM IN LEAD EXPOSURE (CLINICAL AND EXPERIMENTAL STUDIES)

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Actuality. A problem of the part of lead in development of body iron overload is actively discussed in the modern literature. In this, disorders of heme and nonheme iron in the body in lead intoxications is still not sufficiently investigated.

Purpose of the work. To study peculiarities of disorders of heme and nonheme iron in workers, exposed to lead in production conditions as well as to investigate morphological manifestations of hemosiderosis on an experimental model of lead intoxication in rats.

Materials and methods. 19 workers of an art glass factory, aged 42 ± 11 (main group), occupationally exposed to lead as well as 17 workers of the control group, aged 40 ± 14, were subjects on the study. Indices of iron metabolism (transferrin iron concentration [Tf-Fe], transferrin protein concentration [Tf], transferrin saturation [% Tf], ferritin iron [Ft-Fe] and chelatable iron [Df-Fe] concentration in blood, transferrin iron concentration in blood cells, transferrin and ferritin iron concentrations in plasma, iron concentration in serum) were studied, using a quantitative method of electronic spin resonance (ESR). Also, 36 Vistar male rats were used for reproducing a model of acute, subacute and chronic lead intoxication for morphological assessment of iron (III) metabolism
disorders. For this purpose, histological slides were prepared from the liver pieces, filled into paraffin, with the use of microtome and Pearl' reaction.

Results. It is seen that occupational contact with lead results in a significant increase of serum iron concentration, transferrin iron concentration in blood cells and transferrin saturation, promoting development of a body iron overload. The results of experiments is the evidence of this, where development of expressiveness of interstitial hemosiderosis of various degree has been stated.

Key words: lead poisoning, experimental lead intoxication, transferrine, ferritin, hemosiderosis, electronic spin resonance, secondary iron overload

Introduction

Environmental sources of lead are multiple. Lead poisoning is the leading reason of chronic occupational poisonings. An exposure to lead is known to damage the central and peripheral nervous system, hemopoietic, cardiovascular, gastrointestinal, reproductive, hematological systems and kidneys, and increases a cancer risk. A lead poisoning often goes undetected, since many of symptoms, such as stomach pain, headaches, anxiety, irritability, and poor appetite, are nonspecific and may not be recognized as symptoms of lead poisoning.

Plausible mechanisms of lead carcinogenicity include direct DNA damage, inhibition of DNA synthesis or recovery [1]. 99 % of blood Pb is associated with erythrocytes and lead effects on enzymes in the heme biosynthesis pathway includes inhibition of δ-aminolaevulinic acid (δ-ALA) dehydratase (15 mg/dL Pb results in 50 % inhibition of ALAD), coproporphyrinogen (CP) oxidase and ferrochelatase, resulting in impaired heme synthesis and accumulation protoporphyrin in blood and δ-ALA, CP in urine. Lead is a cumulative poison with 27 year half-life in the body [2]. Therefore, a lead poisoning can cause long-term impairments in the porphyrin metabolism. Hypochromic anemia, characteristic feature of the lead poisoning, is known to be accompanied by normal or increased iron content in the body. The problem of body iron overload in hereditary porphyries, nowadays, attracts great attention [3]. Also, there are indications on ferritin iron accumulation in animal tissues in response to lead introduction [4]. A relation between iron and lead transport was also revealed [5]. δ-ALA is known to promote iron release from ferritin and endoplasmatic reticulum [6–8], induces DNA damage in the presence of ferritin [9], causes iron and ferritin accumulation in the liver [7] and in brain [10]. An

intracellular iron pool may be involved into ALA metabolism (a role of IRE-BP in regulation of erythroid ALA synthase expression [11]). There is evidently a need in further consideration of mechanisms of excessive iron contribution to the pathogenesis of lead poisoning.

Only limited data are available on the non heme iron exchange indices in patients with lead poisoning. 82 worker of the crystal glass factory in Ukraine were under investigation, depending on Pb concentration in the air of the working zone of 1 mg/m^3 during 3 months. A diagnosis of chronic Pb intoxication was recognized in 44 cases [7]. We estimated parameters of non heme iron in a group of lead-exposed workers and investigated, whether there was an increase in tissue iron deposition in experimental lead exposure in rats. The aim of the present study was to examine specific part of non heme iron indices in lead poisonings.

Methodology

A set of biochemical parameters and indices of iron metabolism in the group of lead-exposed workers (age 42 ± 11 years) were investigated. Among patients there were individuals involved in producing storage batteries, ceramics manufacture, polishing lead products, painting, type setting, and electronics. A reference group (age 40 ± 14 years) had no association with an increased occupational lead exposure.

In other to characterize non heme iron status, indices of non heme iron exchange were determined by means of a quantitative electron spin resonance (ESR) technique: ferritin iron, transferrin iron, transferrin protein, chelatable iron concentrations, using respective characteristics of ESR spectra [13, 14] (Fig. 1). A concentration of transferrin iron associated with blood cells $[Tf - Fe]_{bc}$ was calculated, using a transferrin iron concentration in blood $[Tf - Fe]_{bl}$ and plasma $[Tf - Fe]_{pl}$, with account of a hematocrit index Ht :

$$[Tf - Fe]_{bc} = \frac{[Tf - Fe]_{bl} - [Tf - Fe]_{pl}(1 - Ht)}{Ht}.$$

Under elevated transferrin saturation, transferrin saturation values determined in plasma and serum samples were shown to be less than respective values determined in the whole blood of the same patients [15]. Under the increased transferrin iron concentration the difference between experimental and reference data, determined in blood and plasma, was statistically significant in contrast to the data determined in serum. Therefore, the analysis of the blood micro samples provided an adequate estimation of transferrin iron concentration, especially at high transferrin saturation.

Concentrations of iron in serum and lead in blood were determined by atomic absorption spectroscopy (5100-PC, «Perkin-Elmer»). The accuracy of AAS analysis was checked by standard solutions. A hemoglobin concentration was assayed by a hemoglobincyanide method. The hematocrit was measured in blood in a heparinized capillary tube and centrifuged.

An experimental lead intoxication in rats was modeled by means of: injection of 1 ml lead acetate in the dose of 0,027 mg per 100 g five times a week during 1, 2 or 3 months into stomach through a stomach pump (a model of a chronic lead intoxication, 36 experimental animals, 6 rats in every group, including control groups of animals); intraperitoneal injection of 1 ml lead acetate in the dose of 0,5 mg per 100 g five times a weak within 3 weeks (a model of sub acute lead intoxication, 12 animals or 6 in a group) intraperitoneal injection of lead acetate in the dose of 6,25 mg per 100 g twice a weak within 3 weeks (corresponds to 1/4 DL_{50} and is a model of an acute lead intoxication with expressed clinical manifestation, 12 animals or 6 in a group).

Control animals received the same volume of the physiological solution. After intraperitoneal injection of hexenal in the dose of 40 mg per kg, and decapitation, sampling of spleen, liver and kidneys tissues was performed. A histochemical investigation of 10 μm microscopic sections was performed with Pearl's staining for revelation of deposited iron localization in tissues.

The data are given as mean ± statistic deviation (SD). The PI=1-p value of Fischer's distribution function was used as a normalized probabilistic measure of differences between experimental and reference data. In the partial case of I = 1 $P_1 = S_{nm}(T_q(x,y))$, where $S_n(x)$ is a Student's distribution function or $P_1 = 1 - p$, where there is a level of significance of «zero» hypothesis.

Results and discussion

In the group of patients with lead poisoning ([Pb]bl = 56 ± 14 mg/dL) hyperferremia was revealed, which exhibited itself in 1,4-fold increase in serum iron

concentration, chelatable iron concentration, determined in blood (1,8-fold, p = 0,05) and transferrin iron concentration in blood cells (2,6-fold, p = 0,0001; Table 1). A statistically significant 1,4-fold increase was also revealed in transferrin saturation in the whole blood.

There are established high reference values of blood lead concentration (28,6 ± 5,0 μg/dL) in the population group with no association with occupational exposure to lead. Previously lower values were reported for control groups, for example 13,4 ± 4,5 μg/dL [16]. Among healthy people, living in the near industrial areas, substantially lower blood lead levels, averaging approximately 3 μg/dL, are observed [17].

The revealed increase in transferrin saturation is caused by the decrease in transferrin protein concentration in blood of patients rather than transferrin iron increase (Table 1, Fig. 2). Statistically significant 1,3-fold decrease was also revealed in transferrin protein concentration in blood in the group of patients with zero post exposition period, resulting in 1,5-fold transferrin saturation increase. In a sampling of

Table

Concentration of Pb, Hb, Ht, transferrin iron concentration [Tf – Fe], transferrin protein concentration [Tf], transferrin saturation %Tf, ferritin iron [Ft – Fe] and chelatable iron [Df – Fe] concentration in blood, transferrin iron concentration in blood cells, transferrin and ferritin iron concentrations in plasma, iron concentration in serum, in a group of patients with lead poisoning, as well as patients with zero post exposition period and with high transferrin saturation (≥ 36%); the character of the experimental data alteration, compared to the reference data (increase ⇧ or decrease ⇩, if occurs) and relationship between experimental data/reference data are given in parentheses

Parameter	Reference data, n = 17	Experimental data		
		n = 19	Zero post exposition period (n = 13)	Transferrin saturation ≥ 36 % (n = 9)
Whole blood				
[Pb], μg/dl	28,6 ± 5,0	56 ± 17 P_1 = 1,0 (⇧ 1,8**)	52 ± 18 P_1 = 1,0 (⇧1,8**)	48 ± 18 P_1 = 1,0 (⇧ 1,7**)
Hb, g/l	137 ± 11	141 ± 12	146 ± 9	147 ± 10
Ht	0,5 ± 0,3	0,6 ± 0,1	0,6 ± 0,1	0,6 ± 0,1
[Tf – Fe], μM	15,7 ± 2,9	17,9 ± 5,6	17,7 ± 6,5	19,1 ± 6,6
[Tf], μM	31,2 ± 7,7	27,1 ± 13,5 (⇩ 0,9)	23,0 ± 9,4 P_1 = 0,9868; (⇩ 0,7*)	19,8 ± 7,5 P_1 = 0,9987 (⇩ 0,6**)
%Tf, %	27,2 ± 6,9	38,1 ± 15,7 P_1 = 0,9867 (⇧ 1,4*)	41,6 ± 14,8 P_1 = 0,9886 (⇧ 1,5*)	49,7 ± 11,1 P_1 = 0,9999 (⇧ 1,8*)
[Ft – Fe], μM	36,1 ± 11,0	101 ± 170 (⇧ 2,8)	65 ± 102 (⇧ 1,8)	76 ± 121 (⇧ 2,1)
[Dt – Fe], μM	4,3 ± 1,6	7,9 ± 5,1 P_1 = 0,9542 (⇧ 1,8*)	6,4 ± 3,7 (⇧ 1,5)	5,1 ± 1,4 (⇧ 1,2)
Blood cells				
[Tf – Fe], μM	5,3 ± 3,8	13,5 ± 6,9 P_1 = 0,9999(⇧ 2,6**)	12,4 ± 6,3 P_1 = 0,9991(⇧ 2,4**)	15,5 ± 5,5 P_1 = 0,9999(⇧ 3,0**)
Plasma				
[Tf – Fe], μM	25,8 ± 4,5	25,4 ± 10,8	28,7 ± 10,9	30,1 ± 12,8
[Ft – Fe], μM	26 ± 22	115 ± 275 (⇧ 4,4)	46 ± 35 (⇧ 1,8)	38 ± 28 (⇧ 1,4)
Serum				
[Fe], μM	22,0 ± 5,7	28,0 ± 8,8 P_1 = 0,9718 (⇧ 1,3*)	28,6 ± 4,3 P_1 = 0,9981 (⇧ 1,3**)	29,0 ± 6,0 P_1 = 0,9916 (⇧ 1,3**)

**p < 0,05; **p < 0,01.*

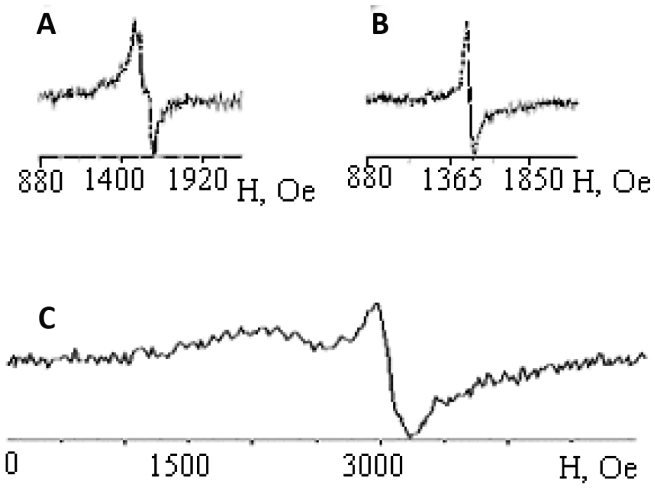

Figure 1. *Fragments of the ESR spectra: a) – iron (III)-apotransferrin complex in human blood: frequency 9,39 GHz, microwave power 70 mW, T 105 K; b) – iron (III)-desferrioxamine B complex in human plasma: frequency 9,39 GHz, microwave power 50 mW, T = 105 K; c) – ferritin iron spectrum, tumour tissue from the patient with glial brain tumour. Frequency 9,30 GHz, microwave power 20 mW, T 145 K. Modulation amplitude 10 G, along the abscissa magnetic field (H) in oersteds (Oe) is shown*

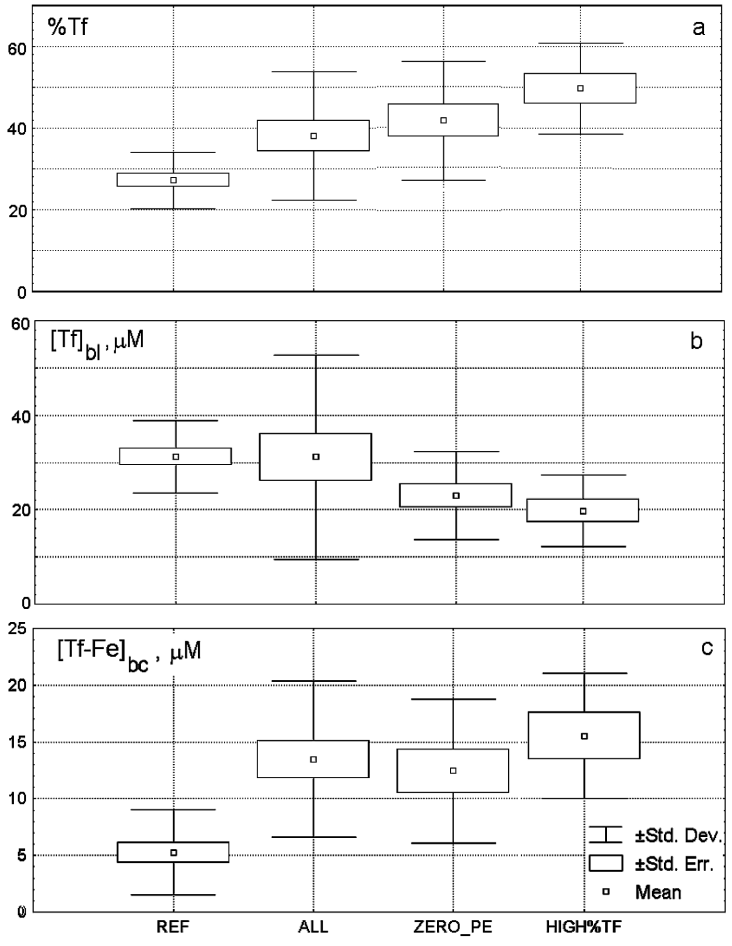

Figure 2. *Box & Whisker Plots of the (a) transferrin saturation and (b) transferrin protein concentration in blood and (c) transferrin iron concentration in blood cells in patients with lead poisoning (ALL), as well as patients with zero post exposition period (ZERO_PE) and with high transferrin saturation 36% (HIGH%TF)*

patients with high transferrin saturation (≥36%) statistically significant 1,8-fold increase in transferrin saturation, compared to the reference data, also occurs, as a result of 1,6-fold decrease of transferrin protein steady state concentration in blood. According to the literature data, suppression of transferrin protein synthesis by lead acetate was previously revealed in human hepatoma *HepG2* cells, whereas acute phase reactants, albumin and human complement C3, were not significantly affected by lead acetate [18].

It is thought that a low-molecular iron weight (LMWI) pool can contribute to tissue damages, in particular, due to amplification of the oxidative stress [19]. Nowadays, mitochondrial inner membrane respiratory enzymes are considered to be the main target of iron toxicity [20]. The recent data confirm that a labile iron concentration is an essential factor, determining the relationship between cell proliferation and apoptosis [21]. Consequently, the size of the LMWI pool or availability of iron for chelation (chelatable iron pool) are of importance for diagnostics and monitoring of states with iron overload and are considered to be more specific indicators of an iron overload than a ferritin protein concentration [22]. In the group of patients with lead poisoning we revealed significant increase (1,8-fold, $p = 0,05$) in the chelatable iron concentration, determined in blood, as compared to the reference data.

Statistically significant increase in transferrin iron concentration in blood cells is also a characteristic feature of patients with lead intoxication (Table 1 and Fig. 2). Taking into account that mature blood cells, including reticulocytes, swallow up transferring iron [23] for heme synthesis in mitochondria [24], the revealed transferrin iron accumulation in blood cells is an evidence of disorders in some links of the heme synthesis chain, rather than iron deficiency in patients.

Figure 3 shows a graph of correlations between nonheme iron indices in the group at patients under investigation. Statistically significant correlation was revealed between a lead concentration in blood and chelatable iron and a cumulated iron concentration in blood.

On the whole, based on the P1 values as a probabilistic measure of the distance between the data (Table 1), indices, determined in the whole blood and blood cells can be considered of as one of the most informative to reveal the difference in iron exchange indices between experimental and reference groups in lead poisonings in humans.

The unequivocal way to reveal a body iron overload is the direct evaluation of the cumulated (ferritin/hemosiderin) iron in tissues. According to a histological study of rat tissues in experimental lead poisoning in the control groups of animals, moderate iron deposits were revealed only in spleen tissues, and predominantly in spleen red pulp, corresponding to the physiologically normal hemosiderin formation, resulting from erythrocyte destruction. Iron in spleen was revealed in the form of insulated granules of the moderate size and fine impurities in reticuloendotelial

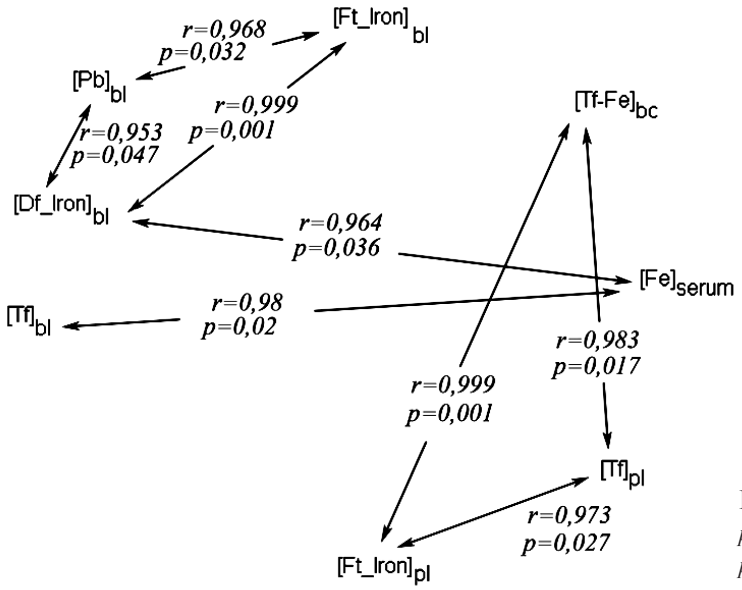

Figure 3. *Graph of correlations between parameters of non haem iron exchange in patients with lead intoxication*

cells. Sometimes, hemosiderin granules were disclosed in the phagocyte cytoplasm, situated in sinusoid openings.

In dynamics of intrastomachal chronical lead intoxication, negligible increase in hystologically revealed iron deposits were found only in the group of animals after 3 months of exposure, which exhibited themselves as an increase in the number of macrophages, containing small and large hemosiderin granules, which can be classified as reticuloendotelial siderosis of a facile degree.

In modeling subacute lead intoxication with low lead dosage given intraperitoneally, sharply expressed iron accumulation was revealed in the reticuloendotelial system and connective tissue stroma of liver, kidneys and spleen (Fig. 2, 3).

In acute lead intoxication in rats, in contrast to the control group of animals and those subjected to chronic and subacute lead intoxication, the expressed iron accumulation was observed in the liver. In histological preparations iron was revealed in the form of small and large homogenous granules in the cytoplasma of reticuloendotelial cells. In the connective liver tissue insulated macrophages were registered with the cytoplasm, filled with small iron rich granules.

Sometimes elastic tissue in liver blood vessels was of blue color. The data obtained are indicative of endogenous hemosiderosis of a predominantly reticuloendotelial type (Fig. 4).

In contrast to the control group of animals, the content of iron in spleen of experimental rats can be characterized as "high". A lot of large irregular shaped granules were observed, predominantly in the red pulp. Hyperplasia of reticuloendotelial spleen cells was observed with numerous Pearl's reaction product granules in cytoplasm (Fig. 5).

Iron staining also revealed homogeneously blue roundish corpuscles in openings of kidney ducts. Sometimes insulated macrophages with small blue granules in cytoplasm were observed in the interstitial tissue of kidneys. Previously, it was established that in rats, received a single, parenteral dose of 1 mg lead per 100 g animal weight, clustering of ferritin next to the dense fibrillar cytoplasmic lesions in kidneys resulted in a selective effect of lead, that requires neither augmented synthesis of ferritin protein nor increased incorporation of iron into preexisting ferritin [4].

The mechanism of lead ability to promote an oxidative stress in lead-exposed tissues remained basically unclear [25]. At least partially, the effect can be attributed to the ability of aminolevulenic acid, accumulated under a lead poisoning, to release iron from ferritin [7, 25] and endoplasmatic reticulum [8] and aggravate, in such a way, an oxidative damage of cell components, including DNA damage [9, 10].

The revealed decrease in transferrin protein concentration and significant increase in a chelatable iron pool in blood and in a transferrin iron concentration in blood cells of patients, as well as an experimental liver, spleen and kidneys siderosis, observed in rats in lead poisoning, are an evidence of apparent iron overload contribution to the pathogenesis of lead intoxication.

Conclusion

In a group of patients with lead poisoning hyperferremia was revealed, which exhibited itself in statistically significant increase in serum iron concentration,

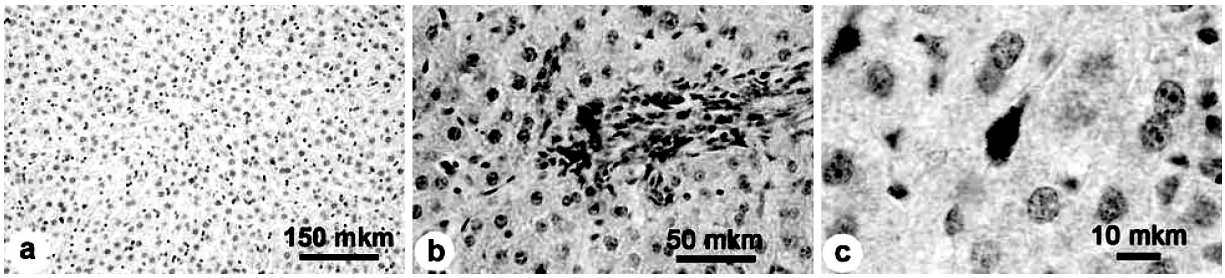

Figure 4. *Histochemical characteristics of rat liver tissue of animals of the control group and animals with experimental acute lead intoxication (intraperitoneal injection of lead acetate in the dose of 6,25 mg per 100 g twice a weak during 3 weeks). Pearl's reaction with nuclei dyeing with aluminous carmine: (a) a control animal, negative iron staining; (b) Pronounced sinusoidal siderosis of the liver from the experimental animal. Iron staining is localized predominantly in reticuloendotelial liver cells; (c) Diffuse blue coloration of cytoplasm of the endothelium of sinusoids and star-shaped reticuloendoteliocytes of liver of experimental animals*

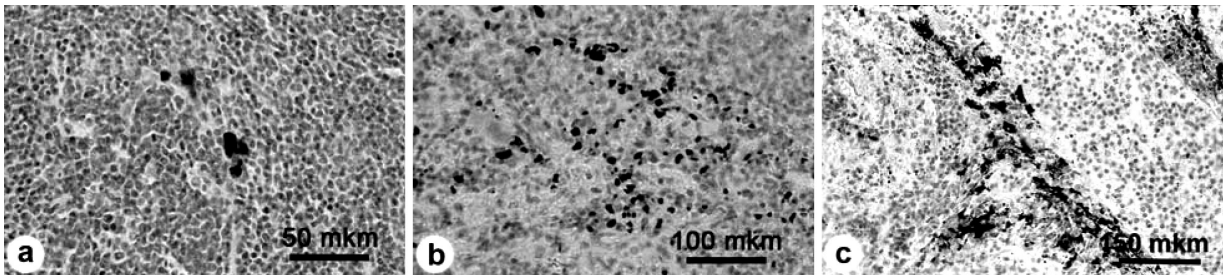

Figure 5. *Histochemical characteristics of rat spleen tissue of animals of the control group and animals with experimental lead intoxication (intraperitoneal injection of lead acetate in the dose of 6,25 mg per 100 g five times a weak during 3 weeks). Pearl's reaction with nuclei dyeing with aluminous carmine: (a) a control animal, moderate localization of iron in solitary macrophages of the spleen red pulp; (b) pronounced hemosiderosis of spleen of an experimental animal with subacute lead intoxication (intraperitoneal injection of lead acetate in the dose of 0,5 mg per 100 g twice a weak during 3 weeks). Macrophages of spleen red pulp with high iron content; elements of connective tissue are impregnated with iron; (c) Pronounced hemosiderosis of spleen from the experimental animal with acute lead intoxication (intraperitoneal injection of lead acetate in the dose of 6,25 mg per 100 g twice a weak during 3 weeks). High iron content in the spleen red pulp*

chelatabable iron concentration, determined in the blood, and transferrin iron concentration in blood cells. Statistically significant increase was also revealed in transferrin saturation in the whole blood. Morphological manifestations of hemosiderosis was registered in the experimental model of lead intoxication in rats.

Thus, the results of clinical observations and experimental studies indicate secondary iron overload manifestations of the body, when exposed to lead. Evidently, determination of iron indices has to be included in diagnostic studies and monitoring of patients with lead intoxication as well as treatment has to be performed with account for the iron overload syndrome in such patients.

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НАРУШЕНИЕ МЕТАБОЛИЗМА ЖЕЛЕЗА ПРИ ЭКСПОЗИЦИИ СВИНЦОМ (КЛИНИКО-ЭКСПЕРИМЕНТАЛЬНЫЕ ИССЛЕДОВАНИЯ)

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Актуальность. В современной научной литературе в последнее время поднимается и активно обсуждается вопрос о роли свинца в развитии перегрузки организма железом. При этом нарушения обмена гемового и негемового железа в организме при свинцовом отравлении остаются не достаточно изученными.

Цель исследования – изучить особенности нарушений обмена гемового и негемового железа у рабочих, экспонированных на предприятии свинцом, а также морфологические проявления гемосидероза на экспериментальной модели свинцовой интоксикации у крыс.

Материалы и методы исследования. Объектом исследования были 19 рабочих завода художественного стекла в возрасте (42 ± 11) лет (основная группа), которые подвергались профессиональному воздействию свинца, а также 17 рабочих контрольной группы в возрасте (40 ± 14) лет. У всех обследуемых с помощью количественного метода электронно-спинового резонанса (ЭСР) в цельной крови, плазме и лейкоцитах изучали показатели обмена железа: концентрацию железа в ферритине, а также концентрацию свободного и связанного с железом трансферрина. Также объектом исследования были 36 крыс-самцов линии Вистар, которых использовали для воспроизведения модели острой, подострой и хронической свинцовой интоксикации с целью морфологической оценки нарушений обмена железа (III). Для этого из залитых в парафин кусочков печени и селезенки с помощью микротома готовили гистологические срезы, на которых проводили гистохимическую реакцию Перлса.

Результаты. Показано, что профессиональный контакт со свинцом приводит к достоверному по сравнению с контролем ($p < 0,05$) повышению концентрации железа в сыворотке крови, в клетках крови – трансферрина, насыщенного железом и степени (%) насыщения трансферина железом, что способствует развитию перегрузки

организма железом. Об этом также свидетельствуют результаты проведенных экспериментальных исследований, обнаруживших в печени развитие различной степени выраженности интерстициального гемосидероза, а в селезенке выраженного сидероза ее красной пульпы.

Ключевые слова: свинцовая интоксикация, экспериментальная свинцовая интоксикация, трансферрин, ферритин, гемосидероз, электронно-спиновый резонанс, перегрузка организма железом

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ПОРУШЕННЯ МЕТАБОЛІЗМУ ЗАЛІЗА ПРИ ЕКСПОЗИЦІЇ СВИНЦЕМ (КЛІНІКО-ЕКСПЕРИМЕНТАЛЬНІ ДОСЛІДЖЕННЯ)

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Актуальність. Останнім часом у сучасній науковій літературі піднімаються та активно обговорюються питання щодо ролі свинцю в розвитку перевантаження організму залізом. При цьому порушення обміну гемового та негемового заліза в організмі при свинцевій інтоксикації залишаються ще не вивченими.

Мета дослідження – вивчити особливості обміну гемового та негемового заліза в працівників, експонованих на виробництві свинцем, а також морфологічні прояви розвитку гемосидерозу при експериментальній свинцевій інтоксикації в щурів.

Матеріали та методи дослідження. Об'єктом клінічних досліджень були 19 працівників заводу художнього скла, віком (42 ± 11) років (основна група), які зазнавали виробничого впливу свинцю на виробництві, а також 17 працівників контрольної групи, віком (40 ± 14) років. У всіх працівників за допомогою кількісного методу електронно-спінового резонансу (ЕСР) у цільній крові, її плазмі та лейкоцитах вивчали показники обміну заліза: концентрацію заліза ферритину, а також концентрацію вільного та зв'язаного з залізом трансферину. Об'єктом експериментальних досліджень були 36 самців білих щурів лінії Вістар, які були використані для відтворення моделі гострої, підгострої та хронічної інтоксикації свинцем для морфологічної оцінки порушень обміну заліза (ІІІ). Для цього з залитих у парафін шматочків печінки та селезінки щурів готували мікротомні зрізи, на яких проводили гістохімічну реакцію Перлса.

Результати. Показано, що професійний контакт зі свинцем призводить до статистично значимого ($p < 0,05$) порівняно з контролем збільшення концентрації заліза в сироватці крові, у клітинах крові трансферину, насиченого залізом, та ступеня (%) насичення трансферину залізом, що сприяє розвитку перевантаження організму залізом. На це також вказують результати проведених експериментальних досліджень, які в печінці щурів виявили розвиток різного ступеня вираженості інтерстиціального гемосидерозу, а в селезінці, відповідно, вираженого гемосидерозу червоної пульпи органа.

Ключові слова: свинцева інтоксикація, експериментальна свинцева інтоксикація, трансфери, ферити, гемосидероз, електронно-спіновий резонанс, перевантаження організму залізом

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