ORIGINAL ARTICLE

CONTENTS

Correction with Omega-3 fatty acid of lead influence on morpho-functional status of rats' cerebral cortex

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ABSTRACT

Aim: Experimental justification for using omega-3 fatty acids to correct the effects of free radical oxidation in the brains of rats with lead poisoning.

Materials and Methods: Experiments were conducted on 24 nonlinear male rats at the age of 3-4 months. Lead intoxication was performed in 16 rats by intragastric administration of plumbum (II) acetate. Part of the animals (n=8) that were given lead intoxication, intragastrically introduced omega-3 fatty acids. Microscopic examination of the cerebral cortex was performed using an Olympus BX-41 light microscope.

Results: Under the condition of lead intoxication, neurocytes of the molecular, outer granular, and pyramid layers had signs of extracellular oedema. The areas of significant haemorrhage in all layers of the cerebral cortex were observed. With correction by omega-3 fatty acids, the microscopic structure of the blood vessel wall was restored. Under the influence of lead, SOD and catalase slowed down the utilisation of hydrogen peroxide, compared to the control group, which mostly normalised with the correction of omega-3 fatty acids.

Conclusions: Thus, studies have shown that under the condition of lead intoxication at a dose of 7.5 mg/ kg body weight for 14 days, histological examination revealed disorders of the cerebral cortex cytoarchitectonics and damage to the structure of the blood vessel walls. With the correction of lead intoxication by omega-3 fatty acids at a dose of 750 mg/kg body weight within 14 days, improvements were noted in the histostructure of the experimental animals' cerebral cortex.

KEYWORDS: lead intoxication; Omega-3 fatty acid; cerebral cortex; neurons, glial cells.

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INTRODUCTION

Chronic lead poisoning is a common problem in both developing and developed countries. The toxic effects of lead on various organs and body systems have been studied for a long time, and the effects of lead intoxication on the hematopoietic system, gastrointestinal tract, liver, kidneys, and reproductive system have been well described [1-3]. Studies have also reported that even small doses (less than 3 μg/dL) of lead compounds (Pb^{2+}) cause central nervous system (CNS) injury and are manifested by a variety of neurological disturbances in the cortex and changes in cortical-subcortical relationships [4, 5]. Exposure to lead intoxication results in the development of acute encephalopathy and peripheral neuropathy, paralysis, toxic coma, reduced cognitive functions and intelligence, and mental disorders [6]. Lead can accumulate in brain tissues by crossing the blood-brain barrier and disrupting the brain's structural components, resulting in injury to glial cells, impaired synapse formation, and disrupted signal transmission [7]. The formation of free radicals has been reported to be associated with increased oxidative stress under lead exposure, which is accompanied by the activation of free radical oxidation processes in cell membranes, lipids and proteins. The lead neurotoxic effect is also released through the displacement of zinc or calcium from compounds enriched with thiol groups, which prevents apoptotic cell death [8, 9].

The morphological changes in the cerebral cortex under lead intoxication, which manifest in the molecular layer nerve cells, include vacuolization, pigmentation, nuclear pyknosis, and dissolution of chromatophilic substance. Foci of haemorrhages, stasis and blood clots characterise severe brain and spinal cord damage forms. There is insufficient information on the lead intoxication pathogenic effect on developing morphological changes in the cerebral cortex ([10]). It may have a protective effect on the central nervous system and serve as a means of preventing various neurological disorders. Confirmation of these facts was the unwinding of the

processes of ω-3 metabolism to eicosapentaenoic acid (EPA), docosahexaenoic acid (DHA), and docosapentaenoic acid (DPA), which have an antioxidant effect: they increase the activity of superoxide dismutase, catalase, reduce the proliferation of neutrophils and the caspase-3 function, increase cellular clearance by macrophages [11-13].

However, the relationship between the high lead concentration in plasma, which damages the nervous system, and the result of correcting the condition with polyunsaturated fatty acids still needs to be studied further. Existing research does not fully disclose cerebral cortex morphology under lead intoxication and the results of its correction.

AIM

The study aimed to provide experimental justification for using omega-3 fatty acids to correct the effects of free radical oxidation in the brains of rats with lead poisoning.

MATERIALS AND METHODS

Experiments were conducted on 24 nonlinear male rats at the age of 3-4 months, weighing 250-280 g. All stages of research are conducted in accordance with international requirements for the humane treatment of animals, as outlined in the "European Convention for the Protection of Vertebrates, which are used for experimental and other scientific purposes" (Strasbourg, 1986).

Lead exposed: 16 rats were intragastrically administered by plumbum (II) acetate in 1% starch solution (in a dose of 7.5 mg/kg body weight) once/day for 14 days. Part of these animals (n=8) were given lead intoxication, intragastrically introduced omega-3 fatty acids (O.N.E. ™ Omega) per 1% starch solution at a dose of 750 mg/kg of body weight once/day for 14 days [14].

The control group consisted of 8 rats that were intragastrically administered an equivalent amount of solvent (1% starch solution) at a rate of 1 ml per 100 g of rat weight over 14 days.

MORPHOLOGICAL RESEARCH

On the 15th day, animals were taken out of the experiment by decapitation under ketamine anaesthesia. The extracted brain pattern was fixed in a 2.5% glutaraldehyde solution at pH 7.2-7.4 in phosphate buffer. It was fixed in an Epon-Araldite mixture, according to the generally accepted method [15].

Demi-thin sections were made from the obtained blocks, and then stained with hematoxylin and eosin. Microscopic examination of the cerebral cortex was performed using an Olympus BX-41 light microscope. We investigated the molecular (plexiform) layer, the external (outer) granular layer and the external (outer) pyramidal layer.

BIOCHEMICAL RESEARCH

On the 15th day, the animals' extracted brains were perfused with a cold 1.15% KCl solution and homogenised at 3000 rpm for 1 minute (Teflon-coated) in a medium of 1.15% potassium chloride (1:3 ratio) for withdrawal. Homogenates were centrifuged for 30 minutes at 600 g, and aliquots of the post-nuclear supernatant were taken into Erpendorf microtubes and stored at -20°C until further processing.

Superoxide dismutase (SOD), catalase, malondialdehyde (MDA), and carbonyl groups of proteins (KGP) levels were determined in brain homogenates, according to the International System of Units recommended for use in clinical laboratory practice.

Statistical processing of measurement results was performed using a software package, including GraphPad Prism 8, Biostat, and MS Excel, and a graph was generated. Statistical analyses were performed using the nonparametric method.

ETHICS

This work complies with the principles of the Declaration of Helsinki.

AI STATEMENT

The author states that no AI tools were used in writing this article.

RESULTS

MORPHOLOGY OF THE EXPOSED RAT'S BRAIN CEREBRAL CORTEX

In the case of lead influence in the molecular layer of the rats' cerebral cortex, the neurocytes exhibited polymorphism phenomena. Their cytoplasm was enlightened, with signs of hydropic dystrophy. Cell nuclei were characterised by hyperchromia. Chromatin in them was usually placed in a lump-shaped region near the nuclear envelope inner membrane. Significant areas of enlightenment were noted around neurocytes, which is a pericellular oedema sign. The glyocytes of the molecular layer under these conditions were also hyperchromic. The latter prevailed, condensed chromatin occupying the eccentric

Table 1. Design groups of experimental animals

Groups	Time, days	Experiment	Animals number
Control	14	intragastric equivalent amount of solvent (1% starch solution at the rate of 1 ml per 100 g of rat weight)	8
Pb	14	intragastric administrated by plumbum (II) acetate in 1% starch solution (in a dose of 7.5 mg/kg body weight 1 time/day for 14 days)	8
Pb+Omega 3	14	intragastric administrated by plumbum (II) acetate in 1% starch solution (in a dose of 7.5 mg/kg body weight 1 time/day for 14 days) + omega-3 fatty acids (O.N.E. ™ Omega) per 1% starch solution at a dose of 750 mg/kg of body weight 1 time/day	8

Source: compiled by the authors of this study

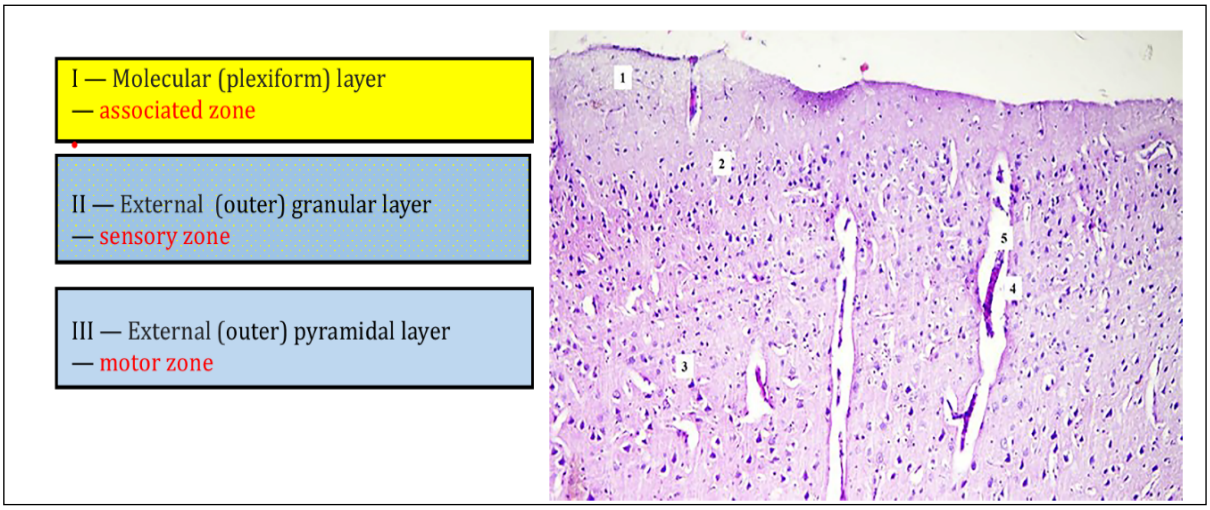


Fig. 1. Histological organization of the cerebral cortex under lead exposed. Molecular layer (1), outer granular layer (2), pyramidal cells layer (3), expansion of the lumen of the blood vessel (4), and blood cells stasis (5). Hematoxylin and eosin x 100
Picture taken by the authors

position. In the molecular and outer granular layers of the experimental animals' cerebral cortex, a significant expansion of the blood vessel lumen was observed in the same experiment. Histological sections revealed blood cell stasis, signs of white blood cell adhesion, and occasionally, the presence of initial blood clots (Fig. 1).

In the outer granular layer of the cerebral cortex, a lesion of the endothelial lining was visualised in the vascular walls. The endothiliocytes were exfoliated from the basal membrane (Fig. 2C). In some fields of view, the fibrin deposition threads on the blood vessels' walls and luminal surface were revealed, and in some places, perivascular oedema manifestations were observed. In the outer granular layer of lead-exposed brain hemispheres, both hyper- and hypochromic cells were noted. Neurocyte nuclei had telocentric localisation, and the presence of binucleated cells was decisive. In the outer granular layer, neurocytes exhibited a significant variation in the nuclear-cytoplasmic index, which may be a possible reaction to the damaging factor's effect. The presence of necrosis areas also characterised this cerebral cortex layer. Various haemorrhage areas were noticeable. In addition, the neurocytes' mitotic activity increased, a compensatory and adaptive response to the influence of plumbum acetate (Fig. 2).

In the experimental group, the animals' cerebral cortex had a pyramid layer with dark cells that predominated. Their shapes and sizes were significantly different. Most pyramidal neurocyte nuclei were hyperchromatic, with a prevailing presence of heterochromatin. Neuronophagia manifestations are often observed, indicating increased functional activity of microglial cells. In some pyramid cells, recesses or niches were formed where glyocytes were localised. It is worth noting that significant changes in the neurocyte nuclei, namely karyopicnosis and karyorrhexis, have been found. A decrease in size, accompanied by hyperchromatosis, was also reported in pyramidal neurocytes. Hromatophilic substance was placed in compact, dark, rod-like formations. Often, pyramid neurocytes were not clearly visualised, as they lost their characteristic shape, their edges were uneven, and the differentiation of the perikaryon, nuclei, and nucleus boundaries was difficult. Ischemic changes in the cerebral cortex's pyramidal layer nerve cells were found.

Microscopic examination of neurocytes revealed the phenomenon of satelitosis, characterised by the

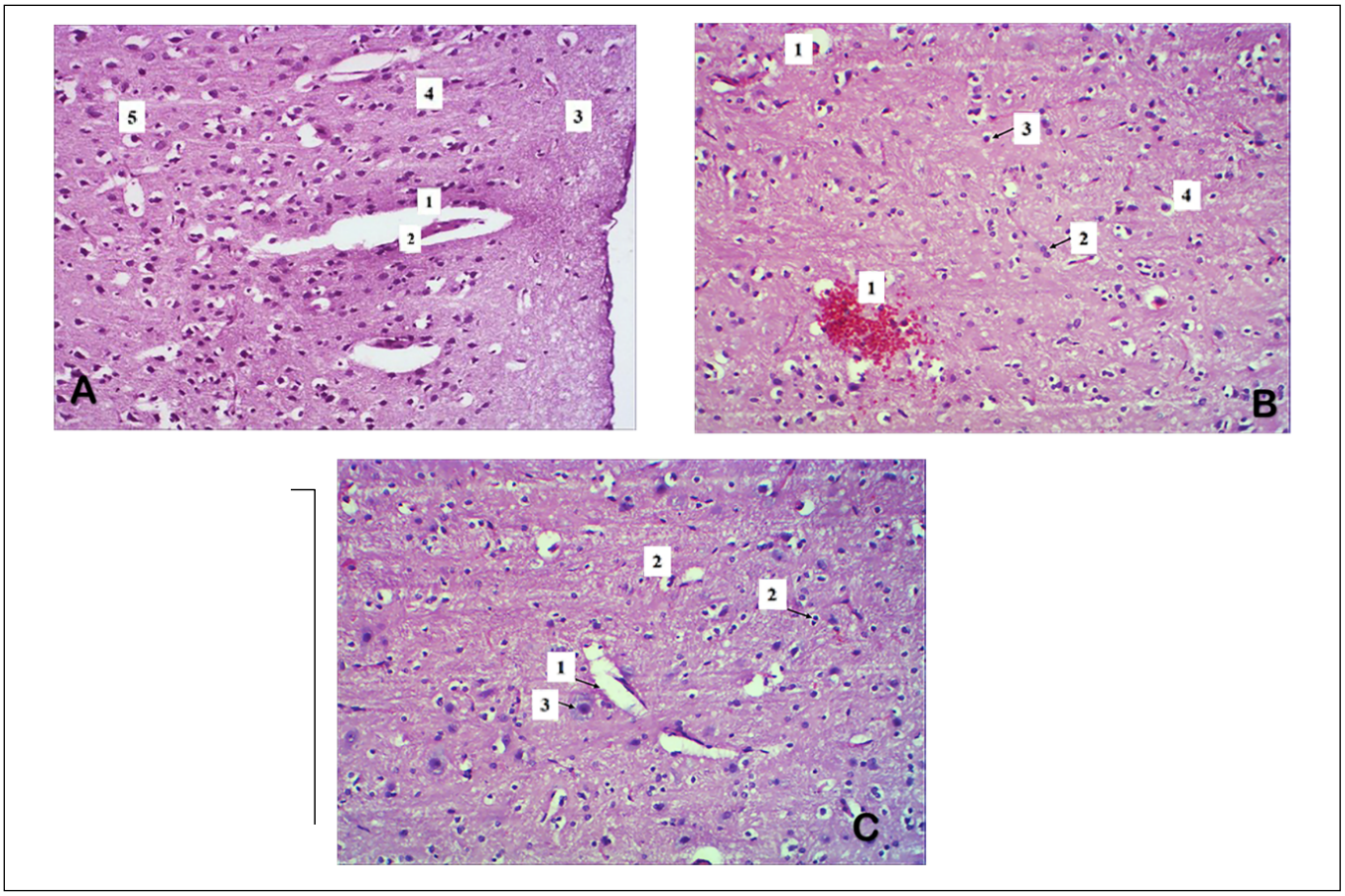


Fig. 2. Microscopic changes of the cerebral rats cortex under lead exposed. A). Perivascular oedema (1), stasis of blood cells (2), molecular layer (3), outer granular layer (4), outer pyramid cells layer (5). B). (1), binucleated neurons (2), vacuolation of the nerve cell cytoplasm and perivascular oedema (3), extracellular oedema (4). C). Endotheliocyte exfoliation of the vessel wall from the basal lamina, fibrin in the lumen of the vessel (1), two-nuclei cells (2), and perinuclear oedema (3). Hematoxylin and eosin. ×100
Picture taken by the authors

presence of glyocytes on the surface of neurocytes. Some pyramid cells also exhibited extracellular oedema signs, as well as cytoplasmic and nuclear hypo- and/or hyperchromasia. Chromatin in such nuclei was diffuse; it was impossible to identify its division into hetero- and euchromatin. The cerebral cortex pyramid layer glial cells showed signs of hyperplasia. Their contours were usually blurred and fuzzy. The cytoplasm of glya cells is enlightened; the nuclei are enlarged and typically contain one nucleolus; chromatin is predominantly diffuse and localised on the nuclear periphery. In addition, the cells with nuclei shifted to the periphery due to hydropic dystrophy of the cytoplasm and perinuclear oedema were detected (Fig. 3).

MORPHOLOGY OF THE CEREBRAL RAT'S CORTEX UNDER LEAD EXPOSURE WITH FATTY ACID OMEGA-3 CORRECTION

At the histological examination of the cerebral rat's cortex under lead exposure with fatty acid omega-3 correction, a decrease in the molecular and external granular layers' blood vessel lumina was detected, compared to the experimental group animals without correction. Destruction of the vascular walls' endothelial layer wasn't shown. A small number of blood elements were recorded in the lumen. The perivascular and extracellular oedema manifestations were moderate. There was a significant improvement in the cerebral cortex cytoarchitectonics. Haemorrhage zones were less common. There are still neuronophagia and satellitosis phenomena on the background of the structural cerebral cortex histological restoration. In some fields of view, the outer granular and pyramidal layers of nerve cells showed signs of necrosis. An essential finding under these conditions was an increase in the activity of the histiocytic row cells in the cerebral cortex pyramidal layer, which is probably the launch of protective mechanisms. These layer glyocytes were characterised by a sharp increase in size compared to those without correction. They were located around or within the body of pyramidal neurocytes and had a high nuclear-to-cy-

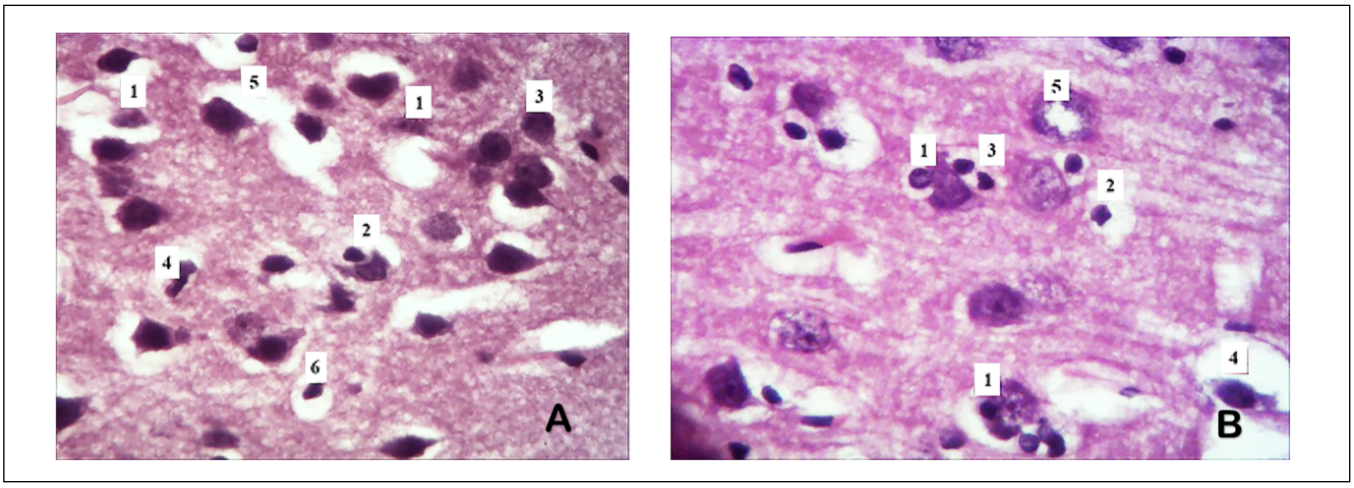


Fig. 3. Histological changes of the cerebral rat cortex under lead exposed. A). Shadow cells (1), neuronophagia (2), karyorrhexis (3), wrinkling pyramidal neurocytes (4), pronounced pericellular oedema (5), karyopyknosis (6). B). Neuronophagia (1), focal neurocyte necrosis (2), satellitosis (3), extracellular oedema (4), karyolysis (5). Hematoxylin and eosin. ×400
Picture taken by the authors

toplasmic ratio. Their nuclei were typically organisation, contained one nucleus, and were surrounded by heterochromatin, which was placed eccentrically (Fig. 4).

BIOCHEMISTRY OF THE CEREBRAL RAT CORTEX UNDER LEAD EXPOSURE AND WITH FATTY ACID OMEGA-3 CORRECTION

Under the influence of lead, SOD (1.44 (1.65; 2.1) conditional units/mg of protein) and catalase (4.16(3.67.4.8) μcat / mg of protein) levels statistically significant decrease compared to the control group ((2.46 (2.11; 2.67) conditional units/mg of protein and 5.92 (5.45; 6.67) μcat / mg of protein, respectively).

The content in the brain of MDA 16.9 (16.3; 17.7) μmol / mg of protein and KGP 6.19 (5.44; 6.55) nmol/mg of protein in this experiment, on the contrary, statistically significantly increases in relation to the control ((11.7 (10.13; 14.48) μmol / mg of protein and 4.19 (4.04; 4.47) nmol/mg of protein, respectively).

The activity of antioxidant enzymes of the rat's lead-exposed brain cerebral cortex is observed during correction by omega-3 fatty acids: SOD level - 2.1 (1.85; 2.27) conditional units/mg of protein, and catalase - 5.34 (4.99; 5.95) μcat / mg of protein. The speed of lipid and protein peroxidation processes slowed down: MDA content was 14.65 (12.8; 1.18) μmol/mg of protein, and KGP was 4.87 (4.68; 5.03) nmol/mg of protein.

DISCUSSION

Under the condition of lead intoxication, neurocytes of the molecular, outer granular, and pyramid layers had signs of extracellular oedema. It can be explained that lead is connected to the endotheliocyte plasmalemma endosurface that damages junctions between endotheliocytes and consequently increases their permeability [16].

Areas of significant haemorrhage in all layers of the cerebral cortex were observed, which may also be associated with damage to the blood-brain barrier [17].

The binucleated neurons were contained in the outer granular layer, which may be an abortive hyperplasia of the nerve cells reacting to unfavourable circumstances [18]. A reduced number of neurons and oligodendrocytes was found in the animal's spinal cord, but an increased number of astrocytes was observed compared with the control [19].

Destruction and, in some cases, nerve cell depletion due to changes in the Nissl substance organisation are observed in the pyramidal layer. The functioning of the chromophilic substance is closely linked to the activity of Nuclear Pore Complex, wich is fundamental for neurons to allow transcription factors to enter into the nucleus [20]. The primary roles of the Nuclear Pore Complex are activation of regulatory elements necessary for adaptation and response to external stimuli, especially those implicated in neuronal plasticity [21, 22].

Neuronophagia, satellitosis, and shadow cells were observed. Shadow cells were described in the case of hematoxylin-eosin staining, like a pale eosinophilic appearance, without nuclear structures, leaving behind bright areas with cytoplasmic silhouettes [23-25]. They were described by several authors (26) as a form of cell death, closely related to apoptosis. It has been proven that lead induces the mitochondrial release of calcium, initiating apoptosis [26].

The glyocytes had perinuclear oedema manifestations. Glia are dynamic cells that sense neuronal meta-

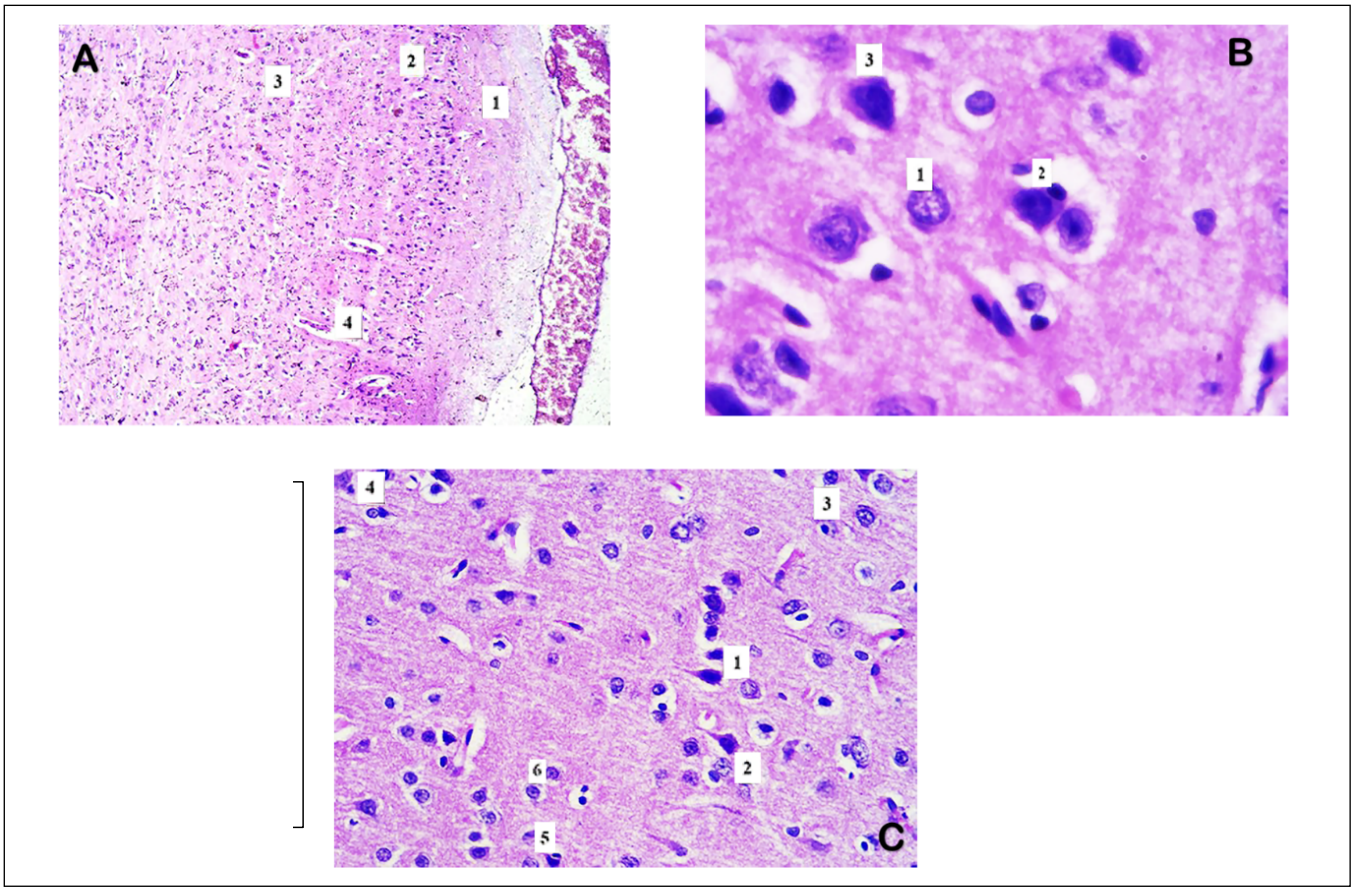


Fig. 4. Histological changes of the cerebral rat cortex under lead exposed with fatty acid omega-3 correction. A). Molecular layer (1), outer granular layer (2), layer of pyramidal cells (3), and lumen of the blood vessel with the molded elements of the blood elements (4). B). Pyramid neurocytes with signs of moderate pericellular edema (1), shadow cells (2), focal necrosis (3), satellitosis (4), neuronophagia (5), microglyocytes (6). C). Glyocytes (1), neuronophagia (2), moderate extracellular neurocyte oedema (3). Hematoxylin and eosin. ×400
Picture taken by the authors

bolic changes and regulate metabolism by transferring metabolites from glia to neurons, such as glucose and lactate, thereby influencing the energy metabolism [27].

All morphological changes depend on different lead-induced neurotoxicity mechanisms, including oxidative stress, alterations in membrane bio-physics, deregulation of cell signalling, and impairment of neurotransmission [28].

Under the influence of lead, SOD slows down the utilisation of hydrogen peroxide with the catalase participation compared to the control group. The peroxidic destruction process increases biomembrane lipids, as evidenced by MDA and KGP, which, conversely, increase in relation to the control. An increase in the intensity of oxidative degradation of cell membrane proteins explains the growth of KGP. The results, confirmed by other authors [29], revealed that lead acetate toxicity induced a significant increase in the levels of BUN, creatinine, and MDA, as well as a significant decrease in SOD and GPx [30]. Lead exposure decreased SOD activities in zebrafish livers due to direct interactions between lead and SOD, resulting in conformational and functional changes of the enzyme [31].

There is no antidote for lead, but it can be removed from the organism with chelation therapy [32]. We can also utilise antioxidants in the alleviation of lead toxicity, including vitamins (Vitamin B6 (pyridoxine), B1 (thiamine), vitamin E (α-tocopherol), and Vitamin C (ascorbic acid)), flavonoids (quercetin and α-lipoic acid), and herbs [33]. Using antioxidant Thiocetam administration, which contains the thiol group, has shown restoration of biochemical and morphological indicators [34].

We use omega-3 fatty acids for correction, and the microscopic structure of the blood vessels' walls was restored, with a reduction in perivascular and periancelular oedema manifestations in the brain hemisphere being characteristic. There were areas of haemorrhage much less often. The phenomena of satellitosis and neuronophagia were stored. There was a significant activation of histiocytic cells, which could be a sign that protective mechanisms are being launched in the cerebral cortex. In the literature, the effectiveness of omega-3 fatty acids in treating and preventing various diseases, as well as their significant

role in combating inflammatory diseases, such as cardiovascular and neurodegenerative diseases [35].

CONCLUSIONS

Thus, studies have shown that under the condition of lead intoxication at a dose of 7.5 mg/ kg body weight for 14 days, histological examination revealed disorders of the cerebral cortex cytoarchitectonics and damage to the walls of the blood vessels. With the correction of lead intoxication by omega-3 fatty acids at a dose of 750 mg/kg body weight within 14 days, improvements were noted in the histostructure of the experimental animals' cerebral cortex.

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CONFLICT OF INTEREST

The Authors declare no conflict of interest

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