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Histological evaluation of the effect of long-term exposure to lead acetate on the cerebellum of albino rats and the therapeutic effect of atropine sulfate

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Abstract

The aim of current study is to investigate the effects of long-term exposure to lead acetate on histological architecture of cerebellum in rat brains. 24 animals were used in the experiment, which distributed to 4 groups, group (G1) control group was administrated by distilled water 1 ml/kg body weight for one month. group (G2) was administrated by lead acetate 12 mg / kg body weight / 10 days for one month. (G3) was administrated by lead acetate 12 mg / kg body weight / 10 days for two months. (G4) was administrated by lead acetate 12 mg / kg body weight / 10 days for three months. The results of the second group showed the disintegration of the nerve fibers and with spongy appearance, with Purkinje cells atrophy in middle layer of the cerebellum and the sloughing of the meningeal membrane on the surface of the molecular layer of cerebellum, while the results of the third group showed presence of disintegration of the nerve fibers and their appearance was in the form of a network that contains congested blood capillaries surrounded by supporting glial cells and wide lumen devoid of any pigment. In addition, the granular layer contains small neurons with pale-staining nuclei and degeneration of the nerve fibers of the cerebellar medulla, while the results of the fourth group showed the occurrence of sloughing of the cerebellar folds from the surrounding meningeal membrane, with congested blood vessels between those folds.

Keywords: Cerebellum; lead acetate; histological changes; Purkinje cells

1. Introduction

The cerebellum is the second largest part of the brain after the cerebrum, and it is considered the most complex compared to its size. It is the smallest hemisphere in the brain. It is located in the back of the brain and is adjacent to its trunk. Inside, it consists of white matter composed of nerve fibers, and outside it consists of gray matter, which is of the bodies of nerve cells, it is called the cerebellar cortex. The wrinkles of the cortex and the adhesion of its wrinkles are tighter than in the cerebral cortex, and its slits are parallel [1]. The cerebellum is connected to the rest of the nervous system by three pairs of cerebral peduncles. The cerebellum contains more than half of the neurons in the brain, although the size of the cerebellum only constitutes 10% of the size of the brain. The cerebellum regulates muscle movement and coordinates it precisely, and also maintains posture. Which the body takes and maintains body balance in all situations and is responsible for voluntary movements [2]. The cerebellum consists of two cerebral hemispheres and a vermis lobe, which resembles a worm as a result of the presence of transverse furrows on its surface that make it divided into worm-like rings [3].

The process of exposure to lead poisoning can occur in any environment, such as the home or the workplace, through the air, dust, food, and water [4]. Cases of lead poisoning are common among humans and animals, and cases of lead

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poisoning can be divided into two types: Acute lead poisoning, which results from exposure to high levels of lead between 3 - 10 mg/m3 in the air over short periods of time. The most important symptoms of poisoning are the appearance of fatigue, vomiting, colic, pain in the abdominal cavity, fainting, constipation, a metallic taste in the mouth, acute encephalitis, stumbling, and paleness in color that is due to anemia, pain in the joints and muscles, nervous agitation, bouts of loss of consciousness, as well as high blood pressure and cases of cancer [5]. The second case is chronic lead poisoning, which results from exposure to low concentrations of lead between 0.5-1 mg/m3 in the air for long periods of time. Its most important symptoms are continuous and severe vomiting and lack of control of movement, which is accompanied by loss of consciousness, loss of appetite, and weight loss. Chronic poisoning may be accompanied by hearing loss, trembling, numbness, anxiety, dizziness, kidney failure, and damage to brain cells [6].

Lead is an effective source of neurotoxicity, and this is clearly evident in pre-school children as a result of abnormal changes in their behavior and actions [7]. One of the most important forms of the severe effects of lead on the nervous system is acute encephalopathy, which occurs as a result of exposure to high concentrations of lead, reaching 80 mg/cm3 of blood, which leads to weak memory, tremors, and nervous spasms that occur with the onset of constipation and then death [8]. It also leads to muscle weakness that later develops into paralysis, which is observed in the form of laxity in the wrist or foot and is a distinctive sign of peripheral nerve disease [9]. Some symptoms, such as headache, lack of concentration, nervous irritability, memory loss, and dullness, are all early symptoms due to the effect of lead on the central nervous system [10]. A study showed that exposure of chicken embryos to lead led to neurological damage that appeared in the form of blood spots in the hind brain, in the dorsal region, and in the tail region, in addition to the presence of deformed and undeveloped embryos as a result of lead's interference with the paths of neuronal development in the embryos [11].

Atropine is a naturally occurring alkaloid (a member of the Solanaceae family). It is a natural compound because it comes from a plant source (such as the plant known as Lady's Nightshade) [12]. The pharmacological composition of atropine can be classified as an anticholinergic drug, a drug that blocks the action of acetylcholine. It is a highly selective muscarinic receptor agonist. Atropine is a World Health Organization (WHO) essential medicine (List of Essential Medicines), a list of the minimum basic medical needs of a healthcare system. It is used as an antiarrhythmic, to dilate mydriasis, to treat convulsions, and to treat poisonings from certain pesticides [13].

Atropine works by knowing how the body responds, affecting the parasympathetic nervous system and, consequently, various organs. It also affects the sinoatrial node, increasing its activity, which generates a reflex in the vagus nerve [14]. Atropine is given to treat bradycardia (an extremely low heart rate) and blocks the transmission of acetylcholine, a neurotransmitter. Atropine is widely used in medicine, particularly in ophthalmology, where it dilates the pupil by preventing contraction of the circular pupillary sphincter muscle, which is stimulated by the release of acetylcholine, allowing the radial pupillary dilator muscle to contract, thus dilating the pupil. It is used in patients with gastric and peptic ulcers, as it reduces gastric and intestinal secretions, and reduces bronchial secretions [15].

2. Materials and Methods:

2.1. Experimental Animal

The animal model which used in current study was Rattus norvegicus to observe the effect of lead acetate on cerebellum of the animals. lead acetate was obtained from Lead acetate was obtained from the chemical storeroom at the Department of biology /College of Education for Pure Sciences at Tikrit University. Experimental animals were obtained from Animal House / College of Veterinary Medicine of University of Tikrit and the experiment accomplished in there. 24 adult rat males of the above type were used in this experiment. Their weights were 250-270 g and their age about 10-14 weeks and distributed into four groups. Lead acetate was use as a causative agent to induce the histological effects, the dose was 12mg/kg/10 days as intraperitoneal injection [16], and Atropine sulfate was used, the dose used was 0.2 ml/kg of the drug, which was given by subcutaneous injection.

2.2. Experiment design

Experimental animals were distributed to 3 groups, each group contain 6 animals, As follows:

- The first group (G1) control group was injected intraperitoneally by normal saline 1 ml/kg body weight for one month.
- The second group (G2) was injected intraperitoneally by lead acetate 12 mg / kg body weight / 1 dose every 10 days for 4 months.

- The fourth group (G4) was injected intraperitoneally by lead acetate 12 mg / kg body weight / 1 dose every 10 days for 4 months, then injected with the drug at a concentration of 0.2 ml/kg for a period of 7 days.

2.3. Histopathology

Transverse sections of the fixed brains were embedded in paraffin wax, and 5 μm sections were routinely processed for histology according to the revised procedures of the National Toxicology Program [17]. A morphological and immunohistochemical study was performed to evaluate both grey (GM) and white matter (WM). The cerebral and cerebellar cortices, thalamus, hippocampus, and cerebellar nuclei were selected as representative GM areas. The corpus callosum, internal capsule, and cerebellar WM were evaluated as WM structures. Other brain structures, such as leptomeninges, choroid plexus, ependyma, and neuroparenchymal vessels, were also evaluated.

3. Results

The histological examination of control group (G1) revealed normal cerebellum texture which appear in three distinct layers, molecular layer, which shows limited numbers of small neurons and glial cells with small blood vessels, middle layer Purkinje cells a single row of cells that appeared and the granular layer contained several rows of small granule cells and glial cell, underneath it the pulp region and white matter contained nerve fibers with supporting glial cells. As shown in Fig1,2.

The molecular zone of the cerebellar cortex contained glial support cells and larger neurons within the spongy zone composed of dissociated nerve fibers, where a spongy pattern with large vacuoles and a foamy pattern with small vacuoles appeared. Purkinje cells within the nodular layer were degenerated and their cytoplasm was pale, the nuclei were unclear, and they were surrounded internally by numerous rows of neuronal and support granule cells Fig 3.

The white matter (cerebellar medulla) contained bundles of dissociated nerve fibers with some glial cells and surrounded by numerous clusters of granule cells whose fibers were intertwined with the nerve fibers from the cerebellar medulla Fig 4.

The molecular zone contained disjointed nerve fibers and a few small neurons, the nodular layer, which was composed of Purkinje cells, appeared atrophied and shrunken, and the granular layer, which had large numbers of rows of ganglion cells Fig 5.

Some ganglion cells (Purkinje cells) were found to be atrophied in the cerebellar cortex between the molecular layer containing small pyramidal cells and the multi-rowed granular layer of small neurons and glial cells Fig 6.

The cerebellar folds contained the three layers: the molecular layer, which contained small pyramidal cells and glial cells in their normal position, and was covered by the meninges, which appeared almost normal, but contained blood vessels that appeared congested; the nodular layer, which contained normal Purkinje cells; and the granular layer, which appeared widespread and multi-rowed, dark-stained cells. The medulla of the cerebellum contained normal nerve fibers, with congestion in some blood vessels Fig7.

The cerebellum medulla contained some congested blood vessels surrounded by bundles of branching nerve fibers containing supporting glial cells, while the adjacent granular layer contained small nerve cells in groups. Purkinje cells were found in large sizes with spherical nuclei and their fibers were continuous with the pyramidal cells in the molecular layer and with the nerve cells in the granular layer.

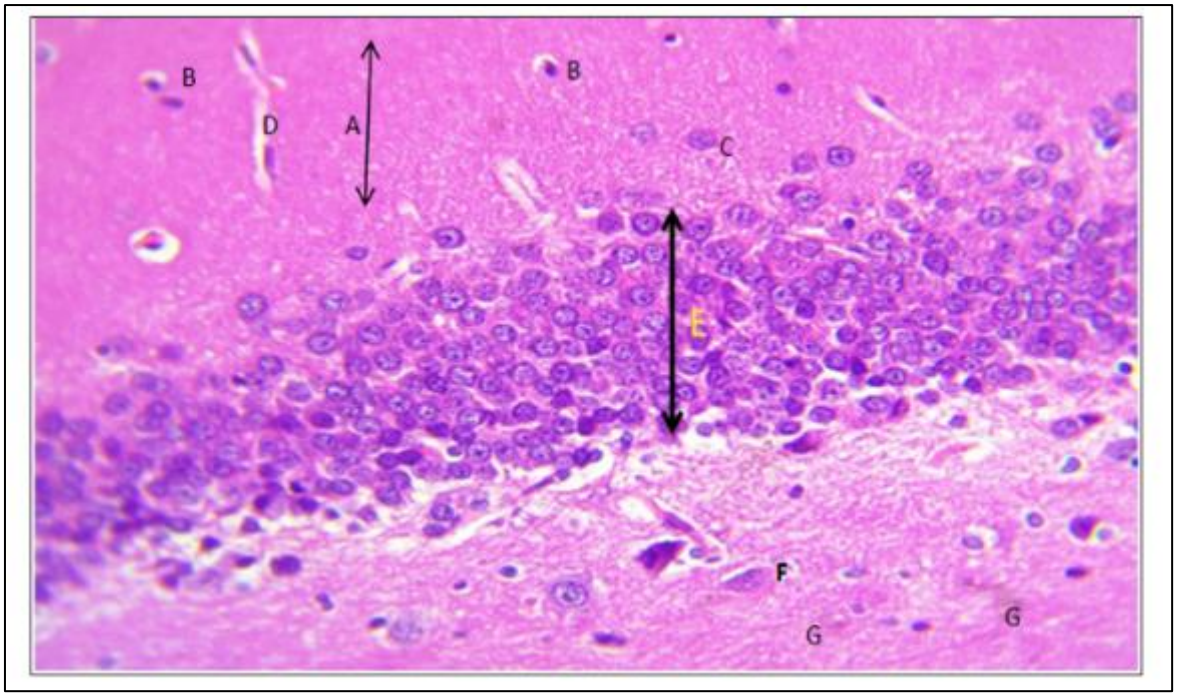

Figure 1 A section of the cerebellar cortex of control group showing the molecular layer (A), which contains glial cells (B), neurons (C), capillaryblood vessels (D), granular layer (E), pyramidal neurons (F), and cerebellar medulla. (G). (H&E 400x)

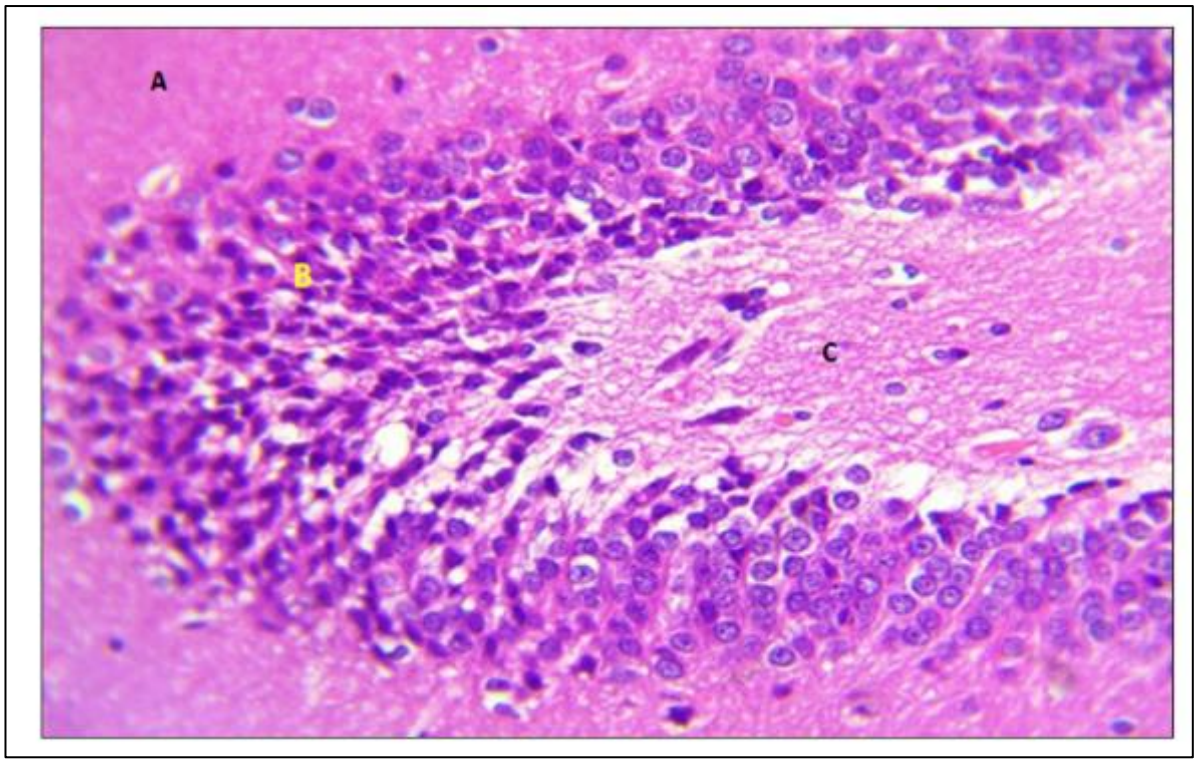

Figure 2 A section of the cerebellar cortex of control group showing the molecular layer (A), the granular layer (B), and the cerebellar medulla(C). (H&E 400x

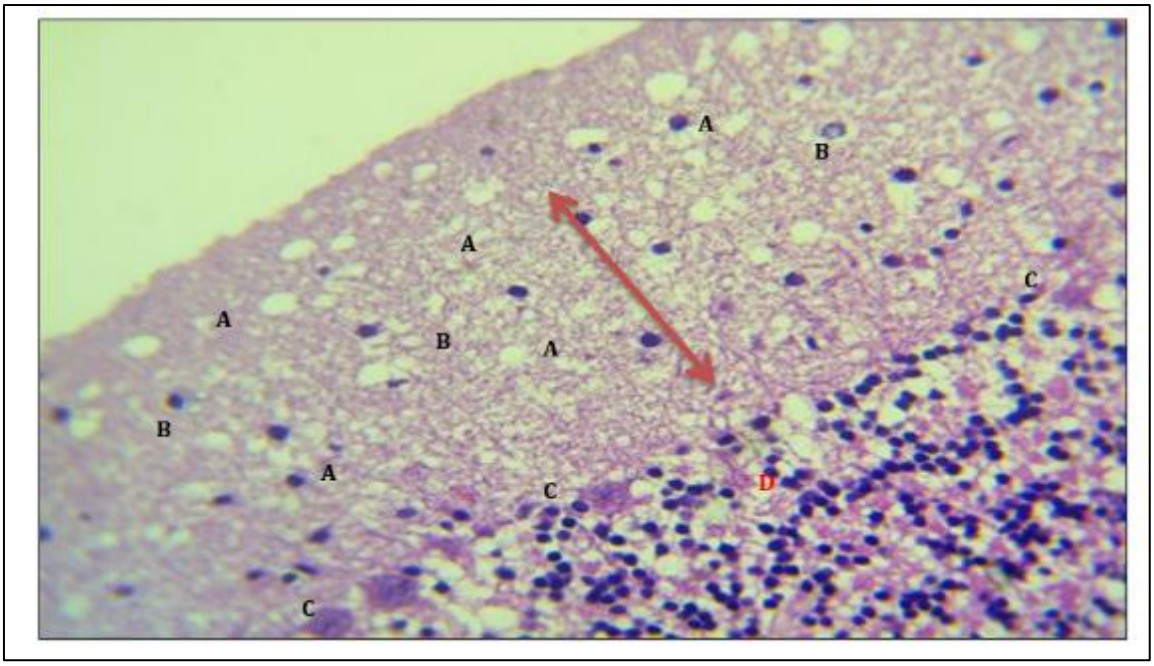

Figure 3 A cross-section of the cerebellar cortex of second group (G2)., molecular layer with spongy and foamy vacuolation of nerve fibers (A), small glial and pyramidal cells (B), Purkinje cell degeneration (C), granular layer (D). (H&E 400x)

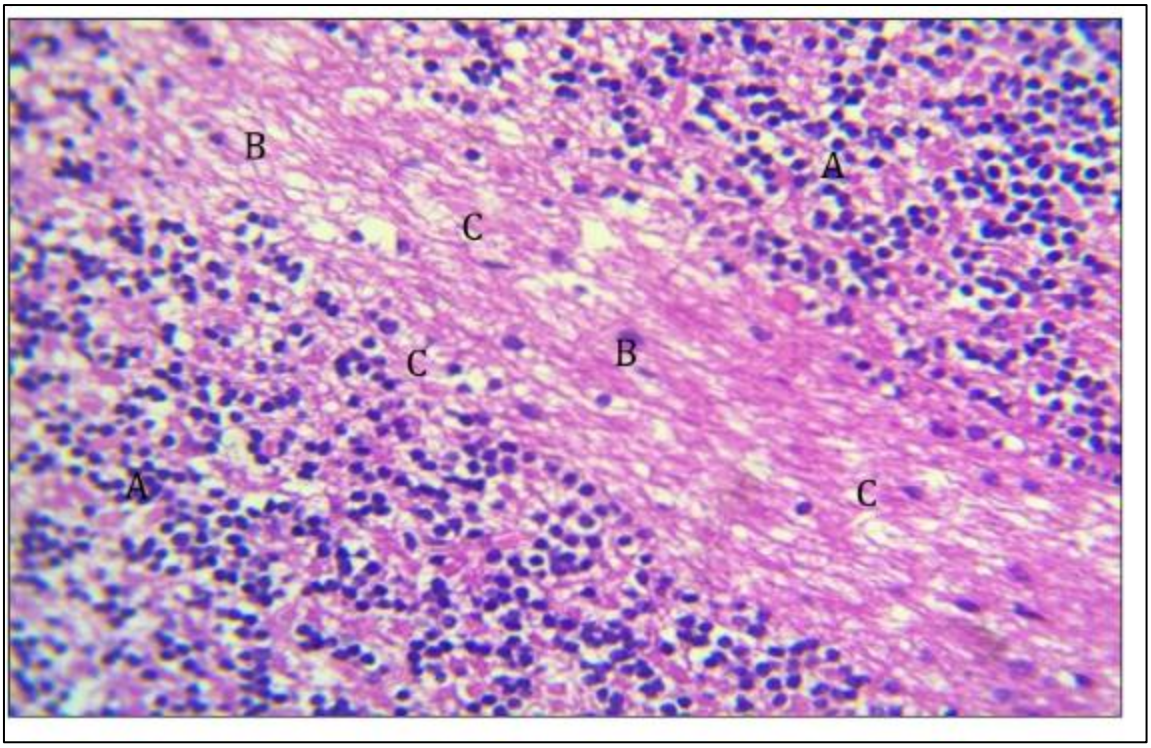

Figure 4 A cross-section of the cerebellar cortex of second group (G2)., granular layer (A), cerebellar medulla with dissociated nerve fibers (B), glial cells (C) (H&E 400x)

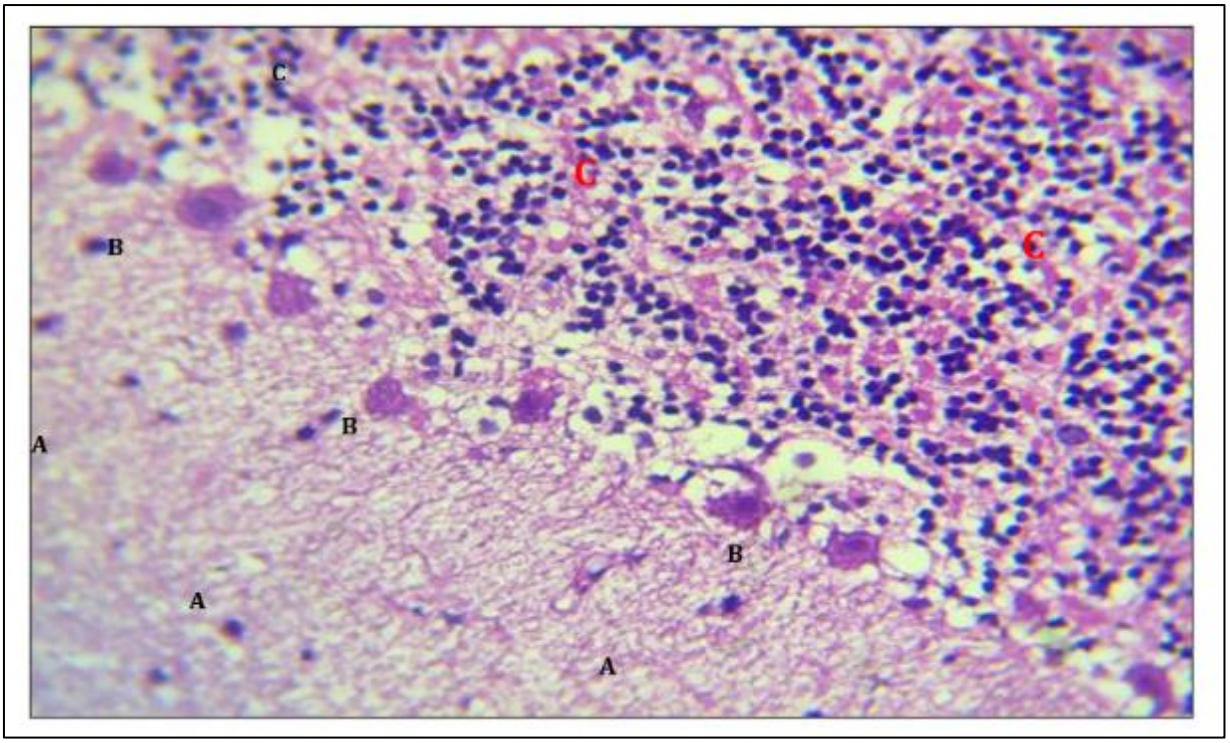

Figure 5 A cross-section of the cerebellar cortex of second group (G2)., molecular layer containing dissociated nerve fibers (A), degeneration and shrinkage of Purkinje cells (B), granular layer containing small neurons and glia (C) (H&E 400x)

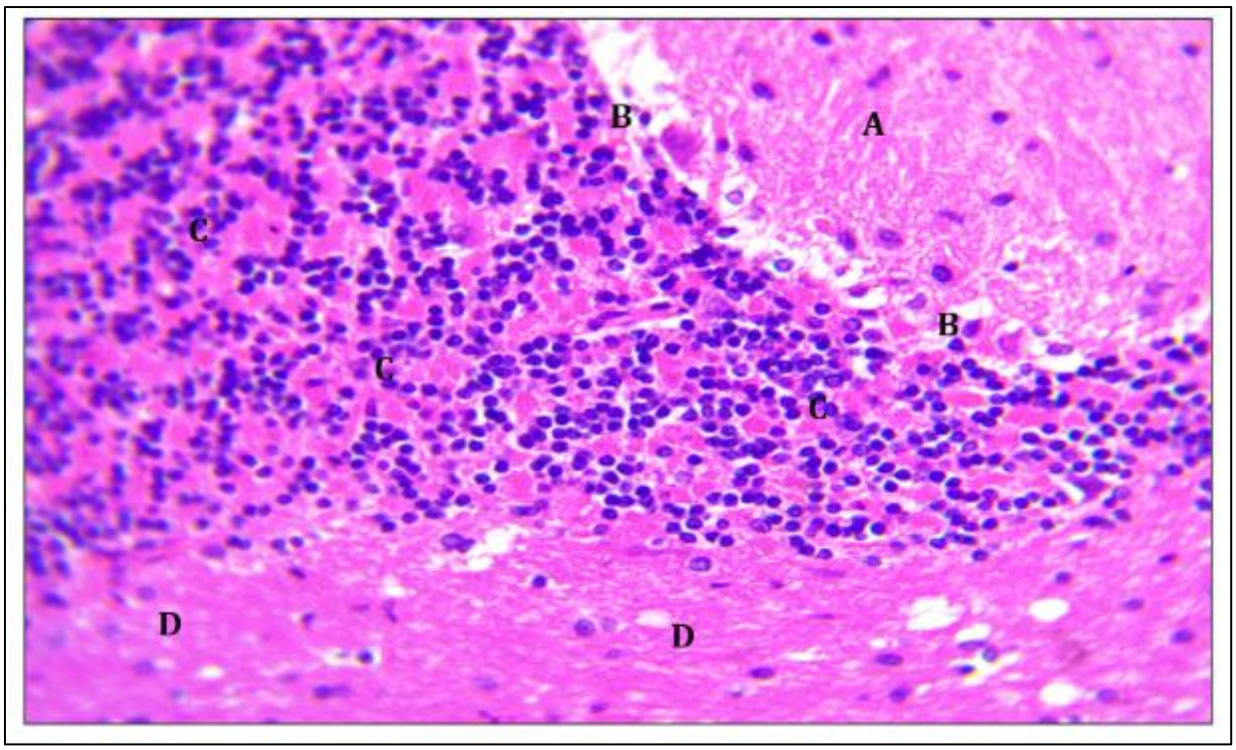

Figure 6 Cerebellar cortex, molecular layer (A), Purkinje cell atrophy (B), granular layer containing neurons and glial cells (C), cerebellar medulla (D). (H&E 400x)

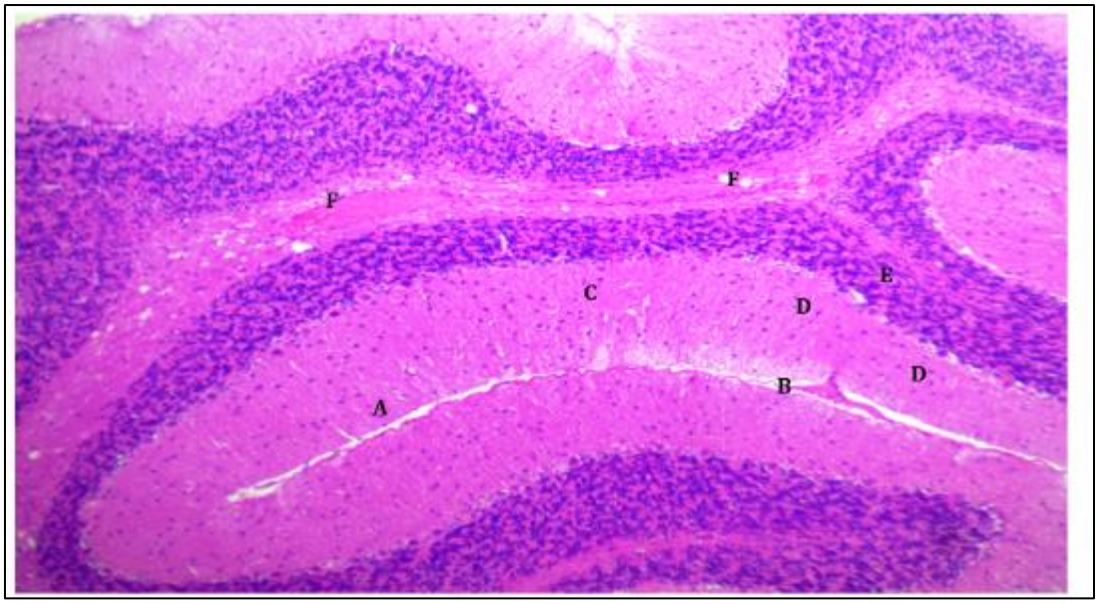

Figure 7 Cerebellum, meninges (A), meningeal vessels (B), molecular stratum (C), nodular layer (D), granular layer (E), cerebellar medulla (F) (H&E 400x)

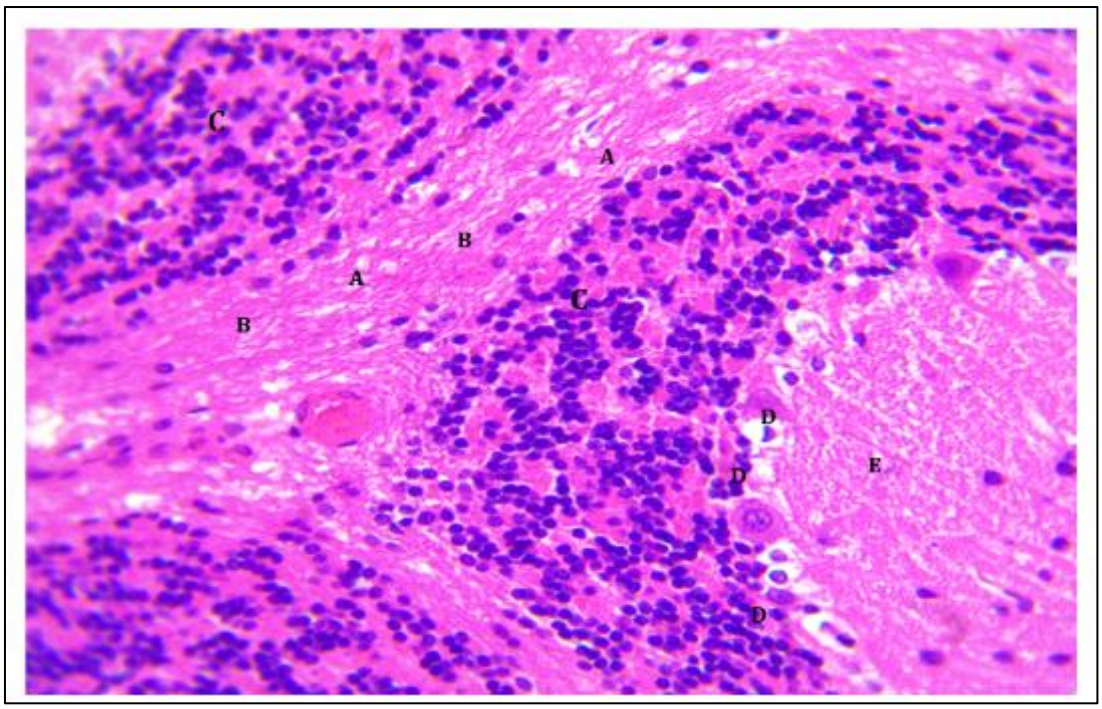

Figure 8 Cerebellar medulla, containing dissociated nerve fiber bundles (A), pyramidal cells and microglia (B), granular layer (C), Purkinje cell layer with constriction (D), molecular layer (E). (H&E 400x)

4. Discussion

The nervous system is the primary target of exposure to lead. It appears that the brain is particularly vulnerable to lead neurotoxicity and can change the binding of lead and the functions of enzymes and proteins in cells. It has been found that exposure to lead significantly reduces the activity of the enzyme acetylcholine esterase (ACHE) and thus leads to a disturbance in function. Cholinergic, which leads to neurotoxicity; [18]. Recent studies have indicated that the activity of ACHE decreases when exposed to free radicals (ROS) resulting from exposure to lead. Lead also has a great affinity

for free S-H groups found in enzymes and proteins, where its association with them leads to a change in their functions, including the activity of the ACHE enzyme and the resulting An increase in the level of acetylcholine (ACH) at the synapse [19].

Lead toxicity usually occurs by generating increased amounts of reactive oxygen species (ROS) and by interfering with the generation of antioxidants [20]. Lead is not a redox active element and cannot play a direct role in those reactions that initiate the formation of ROS [21].

There are many active types of oxygen (ROS) (free oxygen radicals), including superoxide, hydrogen peroxide, and hydroxyl, all of which lead to neurotoxicity. Naturally, the body uses a defense mechanism to limit the deadly effects of these active types (ROS) by using some enzymes to break them down into molecules. Small, harmless molecules of oxygen and water. However, this method of getting rid of ROS is not completely effective as it leaves some reactive waste in the brain to accumulate, which contributes to neurotoxicity and cell death [22].

An increase in free radicals (ROS) means an increase in oxidative stress, thus inhibiting the electron transport chain and a decrease in the formation of energy compounds. The lack of cellular energy causes high levels of oxygen consumption and an increase in the levels of unsaturated fatty acids, as well as a decrease in the levels of non-enzymatic antioxidants and a decrease in the levels of glutathione and enzymatic antioxidants. Inside the nerve cells, which caused neurodegeneration and major congestion in many areas of the brain, and this is consistent with the study he conducted [23].

Exposure to lead can lead to changes in some properties of membranes in the brain, as lead can generate neurotoxic effects by changing some enzymes associated with those membranes [24]. As a result of these toxic effects of lead, which increase the sensitivity of membranes by degrading their components, in addition to directly stimulating the generation of active oxygen species (ROS), and thus causing oxidative stress directly on the main components of biological membranes and on the side chains of hydrophobic fatty acids, unsaturated bonds in fatty acids are considered... Membrane is good sites for lipid peroxidation reactions, and therefore polyunsaturated fatty acids are more susceptible to oxidative damage [25]. This is consistent with the results of the case study, which showed clear and significant damage and disintegration in brain membranes that increased with increasing duration of exposure to lead acetate.

The resulting damage to brain tissue may be due to the effect on glucose metabolism and insulin signaling pathways in the cerebral cortex, as in the study of [26], or perhaps to the inflammation already occurring in the tissue, which caused changes in the composition of fatty acids in cell membranes and their lack of flexibility, thus impeding the formation of... Pseudopods of defense cells and poor ability to absorb pathogens and foreign particles, or an increase in the percentage of histological immune cells may occur, which is an indicator of apoptosis [27].

There has been widespread explosion in many areas of the cerebral cortex, which may be due to the death of programmed cells in the brain tissue and the disorganization of the cortical layers resulting from the exposure of cell organelles to free radicals. There has also been infiltration of a number of glial cells, and large gaps have appeared with accumulated fluids between them, thus forming edema. Which agreed with [28].

The tissues became more affected as the injection period increased, as more widespread swelling appeared in the tissues of the cerebral cortex, with congestion of the capillary blood vessels located between the brain and the meningeal membranes, as well as those located within the cerebral cortex. Noticeable damage also occurred in the nerve fibers, with widespread swelling in the brain medulla region in addition. To the occurrence of the spongy pattern within the pulp tissue, in addition to the infiltration of glial cells, which confirms the occurrence of the inflammatory response within the brain tissue, the occurrence of foamy exudation, which in reality is connective cells filled with proteins and low-density lipids (LDL), which appear foamy upon microscopic examination [29]. and this is completely consistent with the results of the current study. In addition, atrophy occurs in neurons and Purkinje cells, resulting from the loss of some organelles as a result of genetic mutations, exposure to toxic chemicals, or programmed cell death, and this is consistent with the results of the study conducted by [30].

Atropine is a muscarinic antagonist, meaning it prevents the binding of acetylcholine (ACh) to muscarinic receptors in various tissues, including the brain, lead toxicity is known to disrupt neurotransmitter signaling, which induces oxidative stress in the brain, leading to cell degeneration, inflammation, and apoptosis through overstimulation of muscarinic receptors caused by excessive release of acetylcholine (ACh) due to lead poisoning, atropine sulfate helps restore a more balanced neurotransmitter environment, which can reduce neuroinflammation, oxidative stress, and neuronal damage associated with lead poisoning [31].

The ability of atropine sulfate to cross the blood-brain barrier (BBB) may also play a role in mitigating lead toxicity in the brain by penetrating it into brain tissues. Atropine sulfate exerts direct neuroprotective effects or modifies the neurotransmitter imbalance resulting from primary exposure to lead [32].

On the other hand, atropine sulfate contains a sulfate group, which is a chelating agent. Chelating agents are organic or inorganic compounds capable of binding metal ions to form complex ring-like structures called "chelators." Chelating agents have ligand-binding atoms that form either two covalent bonds, or one covalent bond and one coordinate, or two coordinate bonds in the case of diastereomeric chelators. The atoms primarily act as ligand atoms, such as S, N, and O, in the form of chemical groups such as –SH, –S-S, –NH2, =NH, –OH, –OPO3H, or >C=O. Bidentate or polydentate ligands form ring structures containing the metal ion and diastereomeric ligand atoms attached to the metal [33]

Chelation therapy works by binding lead present in the blood and soft tissues, such as the brain, to form a chelator-metal complex. This complex is non-toxic and lipid-soluble, allowing it to cross cell membranes and be excreted in urine and bile [34]. Oxidative stress can be considered one of the main mechanisms contributing to metal toxicity. It has become logical to include chelation therapy and the use of chelating agents capable of eliminating heavy metals, especially lead, which has a high affinity for the sulfur group present in the drug atropine sulfate, to restore affected biochemical parameters to normal [35].

Therefore, the use of atropine sulfate has shown promising results when used to treat the toxic and harmful effects of lead on animal soft tissues. Laboratory, where chelation therapy appears to be the most important and basic clinical treatment in all cases of metal poisoning, and the process of removing a heavy metal is actually the process of binding ions or ligand molecules to a central metal atom or ion through a non-cyclic or ring-like coordination bond. A ligand is a molecule or ion that contains two or more atoms and can easily donate two electrons to form a covalent bond [36].

From all of the above, it can be concluded that atropine sulfate works in two directions. The first is the fact that the atropine moiety acts as an inhibitor of muscarinic receptors, as it binds to them and prevents them from completing the process of stimulating acetylcholine, thus reducing the resulting neural activity by reducing the excessive release of acetylcholine (ACh) resulting from lead poisoning. Thus, atropine sulfate helps restore a more balanced environment for neurotransmitters, which can reduce neuroinflammation, oxidative stress, and neuronal damage. Atropine sulfate exerts neuroprotective effects directly or by modifying the neurotransmitter imbalance resulting from primary exposure to lead [37]. The second approach is related to the fact that the sulfate molecule can be considered as a chelating agent that binds directly to lead to form a stable compound that is easily excreted through the kidneys and bile ducts. Thus, the main pathogen is eliminated, which leads to the termination of all side effects caused by the presence of lead in the various body tissues, in addition to the liberation of self-repair mechanisms and the restoration of the function of the enzymes necessary to stimulate the building reactions in all affected cells and tissues [34].

5. Conclusion

Through the findings of the current study, it was revealed that there were histological changes occurring within the layers of the cerebellum as a result of their exposure to long-term treatment with lead acetate.

Compliance with ethical standards

Acknowledgments

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Disclosure of conflict of interest

The authors declare that there is no conflict of interest.

Statement of ethical approval

All experimental protocols were performed under ethics approval obtained by Tikrit University of Iraq Animal Care Committee (with No.2025.24 Ethical Code)

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