International Journal of Medical Toxicology & Forensic Medicine
2026, Volume 16, E53006

Research Paper

Time- and Dose-Dependent Neurotoxicity of Aluminum Chloride: Oxidative Stress, Cholinergic Dysfunction, and Histopathological Alterations in Male Rat Brain

Hawraa M. Murad[1*], Ghusoon Abdul Kareem Neamah[2], Hasanain Khaleel Shareef[3,4], Ahmed Neema AL-Mussawy[5]

1. *Department of Biology, College of Science, Al-Qasim Green University, Babylon 51013, Iraq.*
2. *Department of Pathology and Poultry Diseases, College of Veterinary Medicine, Al-Qasim Green University, Babylon 51013, Iraq.*
3. *Department of Medical Biotechnology, College of Science, Al-Mustaqbal University, 51001, Babylon, Iraq.*
4. *Department of Biology, College of Science for Women, University of Babylon, 51001, Babylon, Iraq.*
5. *Department of Biology, College of Science. University of Kerbala, Iraq.*

Citation Murad HM, Neamah GAK, Shareef HK, AL-Mussawy AN. Time- and Dose-Dependent Neurotoxicity of Aluminum Chloride: Oxidative Stress, Cholinergic Dysfunction, and Histopathological Alterations in Male Rat Brain. International Journal of Medical Toxicology and Forensic Medicine. 2026; 16:E53006.

https://doi.org/10.22037/ijmtfm.v16.53006

Article info:
Received: 27 July, 2026
Accepted: 11 August, 2026
Published: 23 August, 2026

Keywords:
Aluminum chloride, Oxidative stress, Neurotoxicity, Acetylcholinesterase, Brain, Wistar, Lipid peroxidation, Histopathology

ABSTRACT

Background: Aluminum (Al) is a ubiquitous environmental neurotoxin with a prolonged cerebral half-life. Chronic exposure has been implicated in oxidative damage, cholinergic impairment, and neurodegeneration; however, comprehensive time-course studies integrating biochemical and morphological endpoints remain limited. To evaluate the time- and dose-dependent effects of chronic aluminum chloride ($AlCl_3$) administration on brain oxidative stress markers, acetylcholinesterase (AChE) activity, and histopathological changes in male Wistar rats.

Methods: Ninety adult male rats were randomly divided into three groups (n = 30 each): control (distilled water), low-dose (100 mg/kg b.w. $AlCl_3$), and high-dose (200 mg/kg b.w. $AlCl_3$), administered orally for 30, 60, and 90 days. Brain aluminum residues were measured by graphite furnace atomic absorption spectrophotometry. Oxidative stress biomarkers (MDA, GSH, SOD, CAT) and serum AChE were quantified by ELISA. Brain sections were examined histopathologically with H&E staining.

Results: Brain aluminum accumulated in a time- and dose-dependent manner, peaking at 13.08±0.34 ppm at 90 days in the high-dose group versus 0.014±0.003 ppm in controls. Brain MDA rose from 0.34–0.38 in controls to a peak of 0.88±0.02, whereas SOD (64.80±2.60 to 38.86±1.37), CAT (91.6 to 62.40±3.63) and GSH (8.89 to 2.77±0.71) declined significantly ($P \leq 0.01$). Serum AChE fell from 482.10±0.62 to 112.90±1.21 ΔPh/20 min, a reduction of 76.6%. Histopathology revealed progressive cerebrovascular congestion, perivascular and perineuronal oedema, Virchow–Robin space dilatation, neurofibrillary tangles, and Purkinje cell chromatolysis with neuronophagia.

Conclusion: Chronic $AlCl_3$ exposure induces cumulative, irreversible neurotoxicity through synergistic oxidative and cholinergic mechanisms, underscoring the need for stricter environmental aluminum exposure limits and further investigation of neuroprotective interventions.

*** Corresponding Author:**
Hawraa M. Murad, PhD
Department of Biology, College of Science, Al-Qasim Green University, Babylon 51013, Iraq.
E-mail: *hawraa@vet.uoqsim.edu.iq*

Introduction

Aluminum (Al) is a trivalent metal that occurs in ionic form in most animal and plant tissues and in natural waters [1]. It is the most abundant metal and the third most abundant element in the earth's crust [2]. Urban water supplies contain higher concentrations of Al ions because water is routinely treated with the element before distribution, and dietary Al intake is widespread. Al induces oxidative stress in renal, hepatic and brain tissues, and its cerebral half-life of approximately seven years, together with disruption of neurofilament assembly and axonal transport, allows cumulative damage to develop [3]. Al is an established neurotoxin that accelerates the oxidative deterioration of biomolecules, and its salts contribute to cholinergic terminal degeneration and neuronal loss in the isocortex and hippocampus [4]. Deposition in the cingulate bundle impairs learning [5], the impact of memory impairment caused by Al may also relate to glutamatergic neurotransmission and long-term potentiation in the hippocampus thru the glutamate–NO–cyclic guanosine monophosphate pathway [6].

Cognitive impairment has likewise been attributed to Al-driven oxidative stress and reduced cholinergic activity. Al crosses the blood–brain barrier via specific high-affinity transferrin receptors (TfR) [7], and thereafter perturbs fast and slow axonal transport and provokes inflammatory responses [8].

Malondialdehyde (MDA), a terminal product of lipid hydroperoxide breakdown, is a reliable marker of lipid peroxidation[9]. Cellular defence against free radical damage depends on enzymatic antioxidants, including superoxide dismutase (SOD), glutathione peroxidase and catalase (CAT), and on non-enzymatic antioxidants such as α-tocopherol, ascorbic acid, β-carotene and reduced glutathione (GSH) [10].

Most experimental reports on Al neurotoxicity are restricted to a single terminal time point, so the sequence in which biochemical and structural lesions appear remains poorly defined. The specific focus of the present investigation is therefore the temporal evolution of $AlCl_3$ neurotoxicity: brain Al burden, oxidative stress markers, serum acetylcholinesterase (AChE) activity and cerebral and cerebellar histopathology were measured in the same animals at three exposure intervals (30, 60 and 90 days) and at two dose levels. This design was adopted to establish whether Al accumulation, antioxidant collapse, cholinergic suppression and morphological injury progress in parallel, and to identify the exposure interval at which reversible cellular stress gives way to irreversible neuronal loss.

Materials and Methods

Chemicals

Aluminum chloride hexahydrate ($AlCl_3 \cdot 6H_2O$; catalogue no. A0718; purity ≥99%) was purchased from Sigma-Aldrich Chemical Co. (St. Louis, MO, USA). All other reagents and solvents employed in the work were of analytical grade and used as received. Preparation of the treatment solution The treatment solution was freshlyprepared, by dissolving 2.7 g of $AlCl_3 \cdot 6H_2O$ in 40 ml of distilled water, to obtain the desired Al ion concentration [11]. The $AlCl_3$ being dissolved was given to rats by oral gavage at the following dosages: 100 and 200 mg/kg body mass (b.m.) for the periods of 30, 60 and 90 days [12].

Experimental Animals

Ninety healthy adult male Wistar albino rats (4–9 weeks old, 200–300 g) were used in the study after obtaining them from National Centre for Research and Drug monitoring, Baghdad, Iraq. Before starting the study, the animals were housed for 2 weeks in the animal house of College of Veterinary Medicine, Al-Qasim Green University in normal laboratory conditions. At this time, rats were maintained in clean disinfected polypropylene cages (5 animals per cage) in a room with the temperature of 22 ± 2 °C with a 12-h light/dark cycle and 50–60% relative humidity. Annals standard commercial pellets and clean tap water were provided ad libitum to the animals of all groups throughout the study.

Experimental Design

The 90 rats were evenly divided randomly into three groups of 30 animals in each. Group I (control group) (GI) was given distilled water (vehicle) by oral route during the period of experiment. Group II (GII) was treated with $AlCl_3$ 100 mg/kg b.w. via the oral route daily. Group III (GIII) was administered $AlCl_3$ at a concentration of 200 mg/kg b.w. orally on a daily basis. Ten animals in each group were sacrificed at each time point (30, 60 and 90 days) for further biochemical and histopathological studies.

Determination of Aluminum Concentration in Brain Tissue

Aluminum in the brain was measured by graphite furnace atomic absorption spectrophotometry (GFAAS). The stock standard solution of Al (1000 µg

ml-1 in 2% HNO_3) was diluted serially to obtain working standards of 100, 10 and 1 µg ml-1. Prior to the analysis of samples, a calibration curve was plotted based on these standards.

Brain tissue samples were processed by wet acid digestion according to [13]. In brief, 1.0 g of brain tissue was transferred in a 100 ml conical flask, and 5.50 ml of concentrated nitric acid (70%) and 1.50 ml of perchloric acid were added. The preparation was left at room temperature for an hour and then heated on a hot plate at 100 °C until violet fumes came out. The temperature was increased to 150 – 200 °C and white fumes were evolved. The pale-yellow residual solution was filtered by Whatman filter paper (pore size 0.45 µm) after complete digestion; and the filtrate was diluted to a volume of 25 ml with distilled water which was acidified with 1% HNO_3. The Al content was then determined by GFAAS.

Preparation of Brain Homogenates

At the appointed hour, the animals were sacrificed by chloroform inhalation. The brains were immediately removed, washed in ice-cold phosphate-buffered saline (1× PBS, pH 7.4), and stored at −20°C overnight. Tissue (100 mg) was homogenized in 1 ml of 1×PBS. Cell membranes were lysed by 2 freeze-thaw cycles and the homogenates were then centrifuged at 5000 × g for 5 min at 2–8 °C. The supernatant was harvested and processed immediately or aliquoted and stored at -80°C for analysis at a later time. To preserve the integrity of the samples, freeze-thaw cycles should be avoided.Brain homogenates were prepared as previously described [14].

Blood Collection and Serum Separation

Blood was collected at days 30, 60, 90 from each group by cardiac puncture under terminal anesthesia. The samples were collected in plain tubes (no anticoagulant) and allowed to clot for 30 min. Serum was isolated thru centrifugation at 3,000 rpm for 5 minutes, subsequently aliquoted, and preserved at −20°C until it was needed for assessing AChE activity.

Biochemical Assays

All the biochemical parameters were determined by ELISA using MyBioSource (San Diego, CA, USA) ELISA kits as per the manufacturer's instruction, following double-antibody sandwich procedure, and Executed in the manufacturer's instructions. Following kits were used: (MDA; cat no. MBS738685), catalase (CAT; cat no. MBS701908), (SOD; cat no. MBS036924), glutathione (GSH; cat no. MBS2700076), and (AChE; Cat no. MBS282680).

Preparation of tissue homogenate That's quite a sentence! To be cut and then processed for ELISA, a ~10 mg sample was removed from the tissue to be diced into small pieces and added to 100 µl of PBS for homogenization. The homogenate was centrifuged at 1000 × g (3000 rpm) for 20 min, and the supernatant was then aliquoted for storage at −80 °C until analysis. After completion of the ELISA process, the OD was measured at 450 nm by ELISA Plate Reader, along with Spectrophotometer (UV 2100, Shimadzu, Japan).

Histopathological Examination

Brain tissue for histology was preserved in 10% neutral buffered formalin for a duration of 24 to 48 hours. Tissues underwent fixation and were subsequently processed for dehydration, clearing, and paraffin infiltration using an automated tissue processor (Sakura Finetek, Japan) overnight. The processed specimens were embedded in paraffin wax blocks using an embedding station (Sakura Finetek, Japan) Sample 4 Sections of 5 µm thickness were cut with a rotary microtome (Model: RM2245, Germany) and mounted on pre-cleaned glass slides.

The sections were stained with haematoxylin and eosin (H&E) following the standard procedure of Bancroft and Gamble[15]. Upon drying, stained sections were viewed with a light microscope (Imager A2; Carl Zeiss, Germany) At a 400× magnification, representative photomicrographs were taken via an attached digital camera.

Statistical Analysis

Data were analyzed using Statistical Analysis System (SAS) software. Two-way ANOVA was used to evaluate the effects of treatment and time on the parameters measured, and for further multiple group comparisons, LSD post hoc was applied. Each experimental group consisted of 30 animals (n = 10 for each time point). A probability threshold of $P < 0.05$ was deemed statistically significant.

Results

Residual of AlCl3 in Brain

Brain Al concentrations showed a significant increase ($P<0.05$) in a time- and dose-dependent manner in treated rats compared to controls (Table 1). In GII (100 mg/kg), levels rose from 1.04 ± 0.11 ppm at 30 days to 8.03±0.03 ppm at 90 days. In GIII (200 mg/kg), accumulation was more pronounced, rising from 1.70±0.12 ppm at 30 days to 13.08 ± 0.34 ppm at 90 days. Control values remained negligible throughout (0.014–0.018 ppm).

Brain MDA levels increased significantly (P≤ 0.01) with both dose and duration of $AlCl_3$ exposure (Figure 1). fell from 63.16±1.15 to 56.43±1.60; in GIII, from 52.90±0.75 to 38.86±1.37, compared with controls

Table 1. Consensus Between PSC-17 Screening Outcomes and Clinical Psychological Assessment (N=51).

Group	30 Days	60 Days	90 Days	LSD
GI (Control)	0.016 ± 0.003 ^{Ca}	0.018 ± 0.003 ^{Ca}	0.014 ± 0.003 ^{Ca}	0.011 NS
GII (100 mg/kg)	1.04 ± 0.11 ^{Bc}	3.50 ± 0.23 ^{Bb}	8.03 ± 0.03 ^{Ba}	0.524*
GIII (200 mg/kg)	1.70 ± 0.12 ^{Ac}	4.60 ± 0.16 ^{Ab}	13.08 ± 0.34 ^{Aa}	0.798*
LSD	0.323*	0.573*	0.692*	—

Values are mean ± SD. Different uppercase letters within a column and different lowercase letters within a row denote significant differences (*P ≤ 0.05).

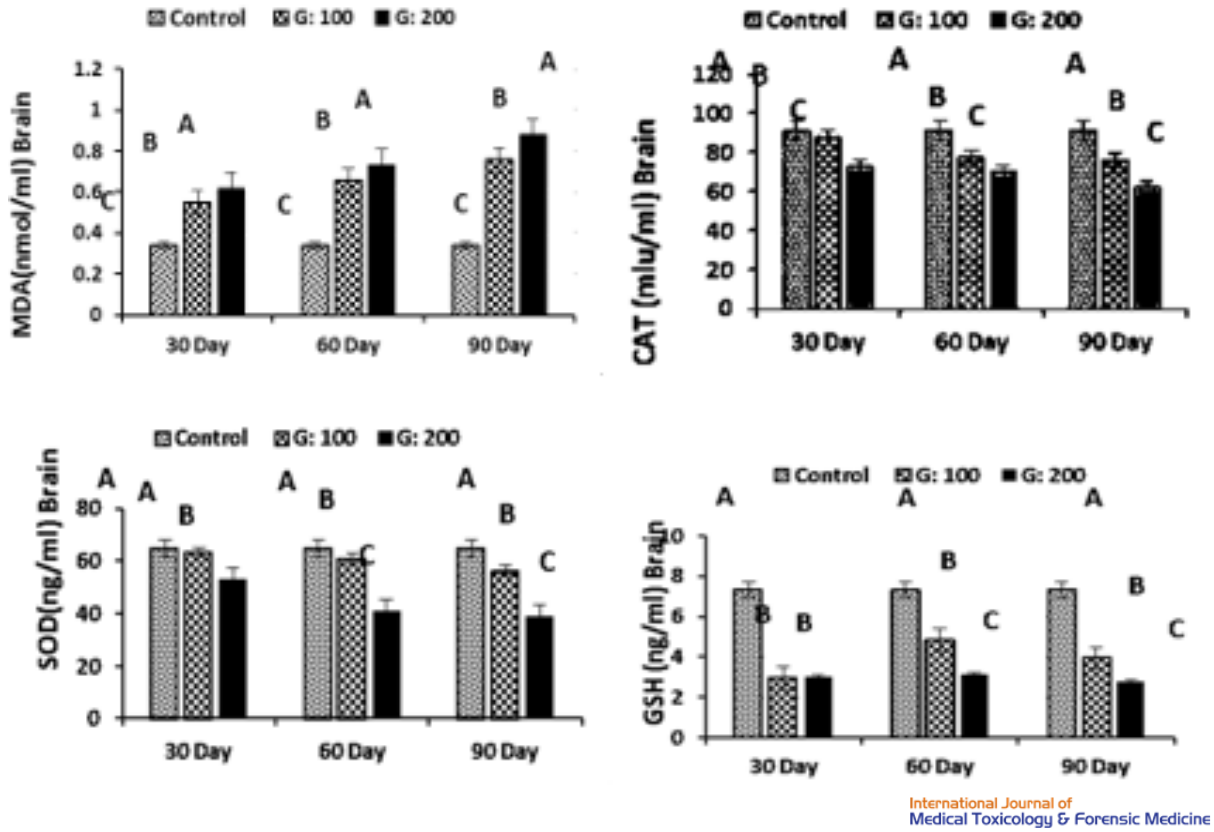

Figure 1. Oxidative stress parameters (MDA, CAT, SOD, and GSH) in brain tissue of male rats following chronic aluminum chloride administration.

In GII, MDA rose from 0.54±0.04 at 30 days to 0.75±0.03 at 90 days; in GIII, from 0.62±0.02 to 0.88±0.02 over the same period. Controls remained stable (0.34–0.38).

$AlCl_3$ treatment significantly reduced brain CAT activity. Values in GII declined from 87.93±0.56 to 76.30±1.24 over 30–90 days, whilst GIII showed a greater reduction (73.13±2.40 to 62.4±3.63) compared with controls (approximately 91.6 throughout).

Brain SOD activity declined significantly (P≤0.01) in aluminium-treated groups. In GII, SOD (64.80±2.60 to 56.43±1.60) (Figure 1).

$AlCl_3$ administration produced a significant decrease (P≤0.01) in brain GSH. Values in GII ranged from 2.97±0.59 to 3.94±0.30, and in GIII from 2.77±0.71 to 3.47±0.46, compared with controls (7.35–8.89) (Figure 1).

Serum AChE levels decreased significantly (P≤0.01) in a time- and dose-dependent fashion (Table 2). In GII, AChE declined from 392.06±0.64 at 30 days to 248.46±0.56 at 90 days. In GIII, a more severe reduction was observed (156.80±0.60 to 112.90±1.21). Control values remained constant (approximately 482.1 ΔPh/20 min).

Table 2. Effect of aluminum chloride on serum AChE (ΔPh/20 min) in chronic toxicity experimental groups.

Group	30 Days	60 Days	90 Days	LSD
GI (Control)	482.10 ± 0.62 ^{Aa}	482.13 ± 0.62 ^{Aa}	482.12 ± 0.62 ^{Aa}	2.16 NS
GII (100 mg/kg)	392.06 ± 0.64 ^{Ba}	326.30 ± 2.31 ^{Bb}	248.46 ± 0.56 ^{Bc}	4.93*
GIII (200 mg/kg)	156.80 ± 0.60 ^{Ca}	141.16 ± 0.43 ^{Cb}	112.90 ± 1.21 ^{Cc}	2.84*
LSD	2.16*	4.82*	2.84*	—
Group	**30 Days**	**60 Days**	**90 Days**	**LSD**
GI (Control)	0.016 ± 0.003 ^{Ca}	0.018 ± 0.003 ^{Ca}	0.014 ± 0.003 ^{Ca}	0.011 NS
GII (100 mg/kg)	1.04 ± 0.11 ^{Bc}	3.50 ± 0.23 ^{Bb}	8.03 ± 0.03 ^{Ba}	0.524*
GIII (200 mg/kg)	1.70 ± 0.12 ^{Ac}	4.60 ± 0.16 ^{Ab}	13.08 ± 0.34 ^{Aa}	0.798*
LSD	0.323*	0.573*	0.692*	—

Values are mean ± SD. Different uppercase letters within a column and different lowercase letters within a row denote significant differences (*P≤0.05).

Histopathological Findings

Cerebrum

Brain sections from GI exhibited normal tissue architecture at all time points (Figure 2). At 30 days, GII displayed severe congestion of cerebral blood vessels surrounded by inflammatory oedema, whilst GIII showed dilatation of Virchow–Robin spaces.

The 60 days result was a dilated Virchow–Robin spaces with perineuronal oedema and activated astrocytes in immediate vicinity to blood vessels in GII. GIII pyramidal cells also contained neurofibrillary tangles and presented intense perineuronal and perivascular oedema.

At 90 days, GII exhibited pronounced meningeal thickening with clusters of microglial cells

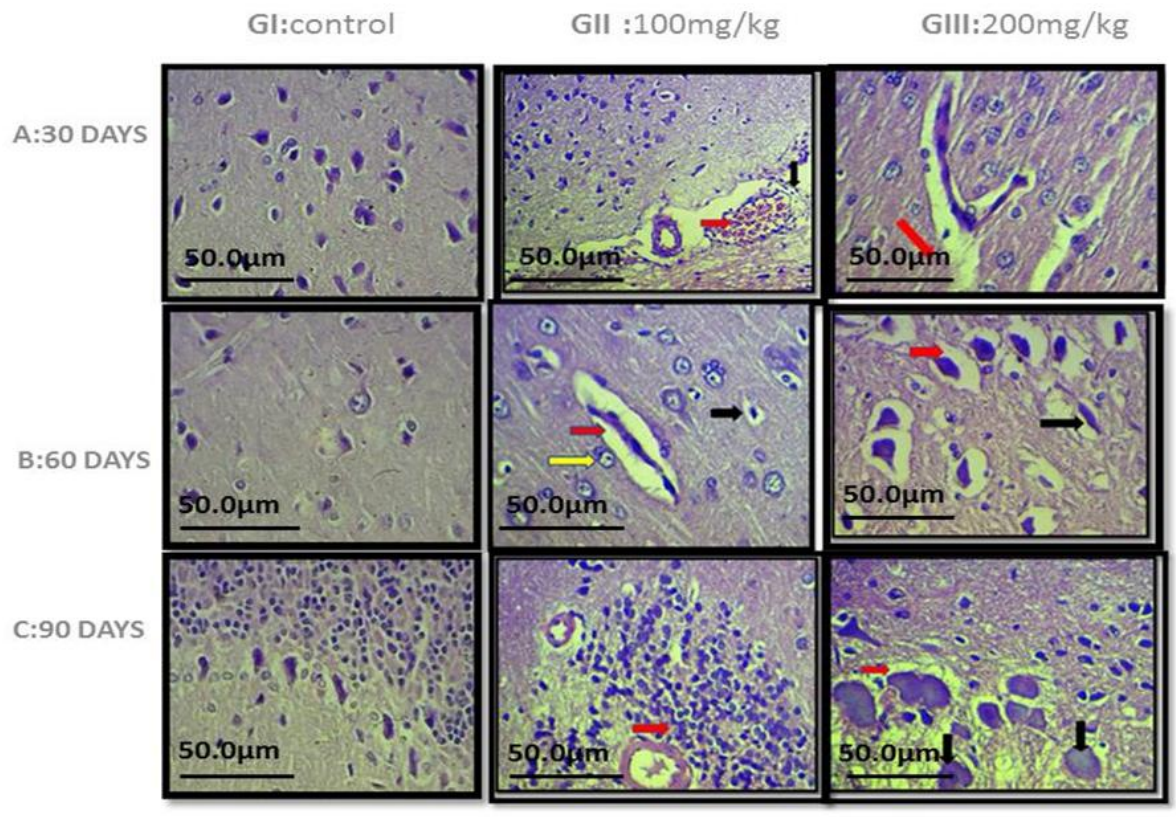

Figure 2. Histopathological sections of rat cerebrum at 30, 60, and 90 days following aluminums chloride treatment (H&E stain, ×400). GI: control; GII: 100 mg/kg b.w.; GIII: 200 mg/kg b.w.

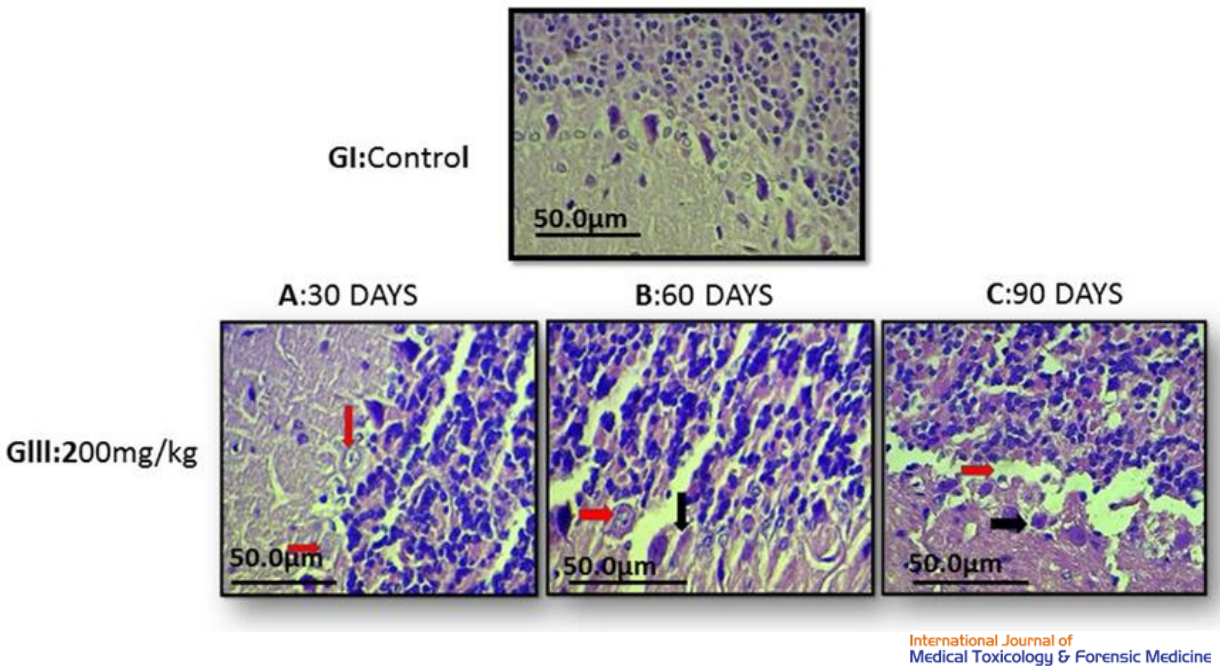

Figure 3. Histopathological sections of rat cerebellum at 30, 60, and 90 days following aluminum chloride treatment (200 mg/kg b.w.) (H&E stain, ×400). GI: control; GIII: 200 mg/kg b.w.

surrounding cerebral blood vessels. GIII showed intense oedema with shrunken neurons, pyknotic nuclei and loss of Nissl substance.

Cerebellum

In GIII, the central chromatolysis neurones at 30 days was observed in cerebellar sections and then central chromatolysis of Purkinje cells with lysis of some were cells at 60 days. At 90 days, marked oedema and central chromatolysis of almost all Purkinje cells were observed (Figure 3). An obvious and quantifiable association was found with increasing time of $AlCl_3$ load (≤90 days) and the exacerbation of brain tissue lesion, hallmarked by further dilation of Virchow–Robin spaces, central chromatolysis, and simultaneous suppression of AChE activity.

Discussion

The present study provides an integrated physiopathological evaluation of $AlCl_3$-induced neurotoxicity by simultaneously assessing brain Al accumulation, oxidative stress biomarkers, cholinergic function and histopathology at 30, 60 and 90 days in male Wistar rats. The findings demonstrate progressive, dose- and time-dependent neurodegeneration mediated by oxidative stress and disrupted cholinergic neurotransmission.

The time- and dose-dependent accumulation of Al in the brain tissue up to 13.08 ± 0.34 ppm in the high dose group at 90 days indicates that Al penetrates the blood-brain barrier and gradually accumulates in the brain tissue. This is in line with Skalny et al., who demonstrated transferrin receptor-mediated endocytosis of Al and regional accumulation in the hippocampus, cortex and cerebellum [16]. In line with this, Al-Hazmi et al. demonstrated that chronic sublethal dose of $AlCl_3$ daily administration led to significant Al deposition in the cerebral cortex of rat that was associated with biochemical and histopathological damage [11]. The extended cerebral half-life of aluminium, which is estimated to be around seven years in humans, impedes removal and justifies the accumulation pattern found in this work[17].

The oxidative stress status determined in the present study exhibited a characteristic antioxidant depletion with increased lipid peroxidation. The marked increase in MDA along with the pronounced decrease in SOD, CAT and GSH suggest that chronic $AlCl_3$ treatment surpasses the internal antioxidant defence mechanisms. These findings agree with Shunan et al., who reported elevated MDA and depleted SOD, CAT and GSH in $AlCl_3$-treated animals[18], and with Zhao et al., who described oxidative stress-mediated neuroinflammation in an $AlCl_3$-induced rat model of Alzheimer's disease [19]. Mechanistically, Skalny et al. demonstrated that Al suppresses antioxidant enzymes by down-regulating the Nrf2/Keap1 pathway while up-regulating pro-oxidant systems such as NADPH oxidase and xanthine

oxidase [16], and Chen et al. reported that Al impairs antioxidant enzyme activity and induces DNA damage in brain tissue [20]. The steady deterioration of oxidative indices between 30 and 90 days in the present study underlines the cumulative nature of aluminium-mediated oxidative damage, which intensifies as tissue metal concentration rises.

The significant dose- and time-dependent decline in serum AChE activity, from 392.06 to 248.46 ΔPh/20 min in GII and from 156.80 to 112.90 ΔPh/20 min in GIII, indicates substantial disruption of cholinergic neurotransmission. This corroborates Obafemi et al., who reported reduced brain AChE activity in $AlCl_3$-treated Wistar rats and related it to Alzheimer-like cholinergic dysfunction [21], and Liu et al., who found that prolonged $AlCl_3$ administration inhibited AChE activity in association with behavioural cognitive impairment [22]. Al may inhibit AChE activity by interacting with the membrane phospholipids, modifying the conformation of membrane bound enzymes, or by binding allosterically at the peripheral anionic site of the enzyme [23]. The gradual decline in activity as the Al burden increases is consistent with the notion that the cholinergic deficit is a consequence of metal deposition and related oxidative membrane damage.

The histopathology showed advancing neurodegeneration associated with both time and dose of exposure. Lesions consisting of marked vascular congestion with inflammatory oedema, dilation of the Virchow–Robin spaces, perineuronal and perivascular oedema, neurofibrillary tangles and neuronal shrinkage with pyknosis of the nuclei suggest aluminium-dependent vasogenic oedema due to an elevation of blood–brain barrier permeability. Similar alterations including neuronal degeneration, vascular congestion and perivascular oedema have been observed by Aboelwafa et al.in the hippocampus of rats treated with $AlCl_3$[24]. Central chromatolysis & Purkinje cell loss were the primary pathological features of the cerebellum, which is consistent with Ghosh et al., who also demonstrated nucleolar prominence loss, eosinophilic swelling along with pyknosis after 90 days of Al administration [25], & with Temitayo et al., reporting chromatolytic PC bodies in the cerebellar cortex [26]. The microglial clustering and astrocytic reactivity at 90 days suggest neuroinflammation, which was Anyanwu et al.blamed on aluminium-induced glial secretion of pro-inflammatory agents such as TNF-α, IL-1β and IL-6[27]. The highlight for the over-representation of Purkinje cells must be noted, since these neurones are also among the most sensitive elements of the central nervous system: the size of their dendritic tree and metabolic and mitochondrial basal demands, the dense expression of glutamate receptors, the limited intrinsic calcium buffering and the modest antioxidant reserves render them particularly susceptible to oxidative and excitotoxic stress, and this may explain why chromatolysis and neuronophagia were more intense and anticipated in the cerebellum than in the cerebral cortex in our observation[25, 26].

Conclusion

The present study demonstrates that chronic oral Al chloride exposure produces progressive, cumulative neurotoxicity along three converging pathological axes: escalating oxidative stress, deteriorating cholinergic neurotransmission and advancing structural neurodegeneration. The parallel association between rising brain Al burden and worsening biochemical and histological indices indicates that accumulation eventually exceeds cerebral detoxifying capacity, so that reversible cellular stress progresses to irreversible neuronal loss. Simultaneous disruption of antioxidant (GSH, SOD, CAT) and cholinergic (AChE) systems suggests that these mechanisms act synergistically rather than independently. Results demonstrating marked vulnerability of Purkinje cells and the appearance of neurofibrillary tangles at higher doses and longer durations have translational relevance, since similar lesions are a hallmark of human neurodegenerative disease. Taken together, these results indicate that a single time point evaluation cannot reflect the entire progression of Al-mediated neuronal damage in the brain and motivate longitudinal surveillance of cerebral Al load in neurotoxicological studies.

Ethical Approval

The research was an ethical approval certificate (no.qgec/8/2025) from AlQasim green university.

Acknowledgment

None.

Funding

This study did not receive any outside support.

Conflicts of Interest

The authors indicate that there are no conflicting interests to disclose.

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