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Folic acid improve developmental toxicity induced by aluminum sulphates

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ABSTRACT

Aluminum sulphate has a significant toxic effects for humans. Aluminum is one of the most abundant metal on the Earth crust. The purpose of this study is to evaluate the effects of short term exposure to aluminum sulphate on the bone development of the fetuses in rats, and if folic acid has a protective role upon that effects or not. Forty female rats were used, ten per group, GI served as negative control (receive nothing except normal feeding and water), GII served as positive control (receive water by gastric gavage), GIII treated with aluminum sulphate orally by gastric gavage and GIV treated with aluminum sulphate with folic acid. Mating occurred and known by presence of vaginal plug in the female rats. Rats were killed on day 18 of gestation. Results: The female rats weight were significantly reduced in the treated group if compared with the control group ($p > 0.001$), all parameters of the fetuses, fetal weight, malformation and the crown rump length reduced significantly p value were <0.000, <0.001, and <0.000 respectively. In histopathological results the aluminum treated group showed severe limited area of preossfication in fetuses vertebrae. Folic acid gave a protective role for all the hazardous effects of aluminum sulphate and prove the diameters measured and also the histopathological effects. Conclusion: Aluminum sulphate can produce hazardous effects on bone of the fetuses, which may affect the life style of these fetuses later on. Folic acid might give a protective role and so should be given to females who tried to conceive.

1. Introduction

One of the most abundant metal on the Earth crust is Aluminum which constitutes of 8.13% (International Programme on Chemical Safety, 1997; Hirata-Koizumi et al., 2011). It is considered as a toxic metal for human body especially the central nervous system, it also affect the skeletal system, brain tissue and blood cells (Dominigo, 1995; Mestaghanmi et al., 2002; Malekshah et al., 2005).

The main route of human exposure to Al is through food (e.g., cereals, vegetables, fruit, and meat) and its compounds in food processing, packaging, and storage, especially Al-based food additives (International Programme on Chemical Safety, 2007; Aguilar et al., 2008; Yu et al., 2016).

People can be exposed to AL by inhalation in certain occupations, such as welding, aluminum soldering and production of abrasives (Hjortsberg et al., 1994); its salts are artificially added to various food products (acidity regulator, raising agent, anti-caking agent, etc.) (International Programme on Chemical Safety, 2007).

Aluminum salts are widely spread as flocculants in the treatment of drinking water to reduce organic matter, color, turbidity and microorganism levels (World Health Organization, 2008), which may lead to increased aluminum intake by humans and animals. Total dietary exposure to aluminum, including exposure via drinking water, has been assessed by FAO/WHO Expert Committee on Food Additives (JECFA) who estimates that the mean total dietary exposure of the adult population ranges from 14 to 280 mg Al/week (International Programme on Chemical Safety, 2007).

In Egypt the river Nile is the main source of drinking water, but its water shows a lot of various Phytoplankton. These treated by adding aluminum sulphate and aluminum oxide to the drinking water (Shehata et al., 2008; Al Zubaidy et al., 2011).

Following ingestion Al absorbed in the blood is eliminated by the kidneys and excreted in urine. The secondary minor role of excretion is via liver and bile (Sutherland and Greger, 1998). So, chronic exposure makes Al accumulated in both kidney and liver (Gonzalez et al., 2004). It can alter the activities of antioxidant enzymes, and leads to various biochemical and physiological dysfunctions in liver and kidney (Nehru and Bhalla, 2006).

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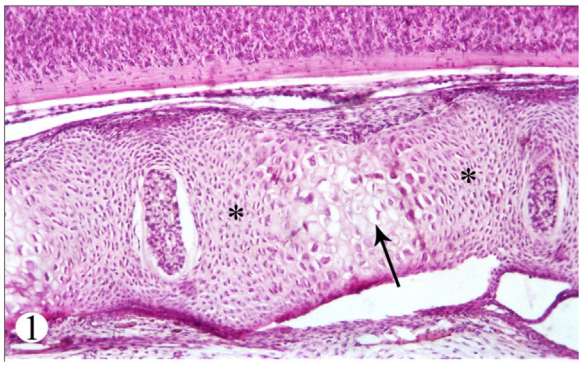

Fig. 1. A photomicrograph of a longitudinal section (L.S.) in a lumbar vertebra of eighteen days old embryo of a control rat showing preossification in the middle part of the body (arrow). Note the cartilaginous distal and proximal parts (*). H&E × 100.

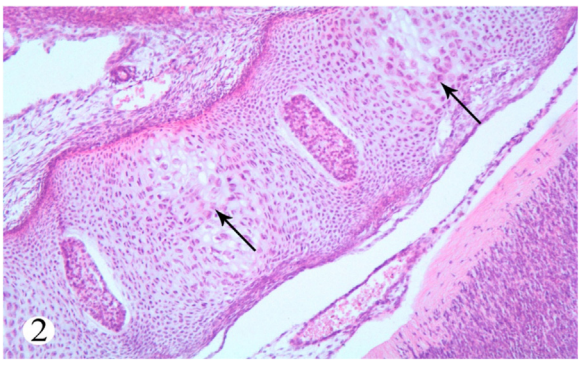

Fig. 2. A photomicrograph of L.S. in a lumbar vertebra of eighteen days old embryo of a rat treated with aluminum (AL) showing a limited area of preossification in the middle part of the body (arrows). H&E × 100.

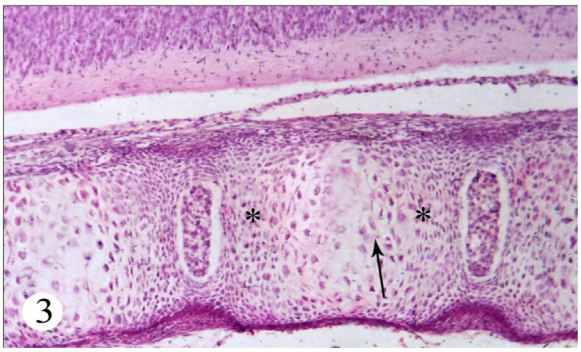

Fig. 3. A photomicrograph of L.S. in a lumbar vertebra of eighteen days old embryo of a rat treated with both AL and folic acid showing preossification in the middle part of the body (arrow) with cartilaginous distal and proximal parts (*). H&E × 100.

Once AL absorbed from the gastrointestinal tract, it is distributed into most organs of the body and accumulates mainly in bone at high-dose levels and passes the blood brain barrier (World Health Organization, 2003).

Folic acid (folate) is a water-soluble vitamin and essential for cell replication. It is a cofactor in one-carbon transformation for methylation reactions in the body. Disturbances in this reactions impair biological pathways such as

synthesis of protein and DNA and repair of DNA (Mattson et al., 2002; Mattson, 2003).

It was suggested that folate has an effect in preventing neurodegenerative diseases, i.e., Alzheimer's disease, Parkinson's disease, and some psychiatric disorders (Solfrizzi et al., 2003; Baydar et al., 2005).

Meta-analysis of several large multicentre randomised controlled trials (RCTs) that supplementation with folic acid daily, alone or as part of a multivitamin preparation during the periconception period reduces the risk of neural tube defects (NTD) in the babies (De-Regil et al., 2010; Zhang et al., 2016).

The present study designed to investigate toxicity of Aluminum sulphate on the bone of fetuses and if there is a protective role of folic acid on aluminum sulphate toxicity. Few studies were done to explore the effects of aluminum sulphate on bone especially vertebrae of the small pups in the first generation, and if folic acid has a protective effects on that or not.

2. Material and methods

2.1. Chemicals

Aluminum sulphate (AS) 98.5% was purchased from Sigma Chemicals Co. AS kept in cool and dark containers every day. Folic acid 5 mg tablets were purchased from pharmacy.

2.2. Treatment protocol

Forty female rats were purchased from Animal house, Faculty of Medicine Assiut University, were divided randomly in different eight cages five female rats each, and after that two male rats added to each cage. Throughout the study, rats were maintained in controlled room temperature (22 ± 3 °C) and humidity. Light was provided on a 12 h light/dark cycle. All animals were fed ad libitum with a standard rat diet and were supplied with drinking water. Mating known by presence of sperm in vaginal smears and considered as day 0. Group I (10 female rats) served as negative control group, received nothing except normal diet. Group II (10 female rats) served as positive control group, received water by oral gavage from day 0–18 of gestation. Group III (10 female rats) treated group received aluminum sulphate in dose equal to 1/10 LD_{50} which is 193 mg/kg (oral LD_{50} for rats equal to 1930 mg/kg) according to (GAC Chemical corporation, 2015), from day 0 to day 18th of gestation by oral gavage. Group IV (10 female rats) received aluminum sulphate in the same dose as group III in addition to folic acid 5 mg/kg/day dissolved in water by oral gavage (the dose which is commercially available) daily one month before the beginning of the study and maintained till the end of day 18th.

Necropsy was performed on day 18 of gestation under light ether anaethesia for the observation of pregnant uteri and collection of the fetus in 95% ethanol to examine the vertebrae. Weight of the female rats, the numbers of fetuses, number of live fetuses, number of resorptions and weight of fetuses were recorded. Then vertebrae taken for microscopic Hematoxyline and eosine examination.

2.3. Statistical analysis

All data were analyzed by using SPSS program version 16, and data compared by using Student T test and One way anova test.

3. Results

3.1. Tabulations

This study was performed to evaluate the toxic effects of aluminum sulphate on the pregnancy of rats and the its effects on the 1st generation of rats vertebra, also evaluated the protective role of folic acid on the toxic effects of aluminum sulphate if given a period before pregnancy.

Table 1 and Fig. 7 show that the mean weight of the female pregnant rats throughout the period of the study 18 days in mg. There were highly significance differences between the weight of the female rats in GI and GII control groups and the treated group