Perinatal Toxicity Of Aluminum

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Citation

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Abstract

In the modern life, the exposure to aluminum is inevitable. Though the toxicity of aluminum was noticed long back, it was not well established. Conclusive evidences about aluminum induced pathologies or pathological consequences linked with aluminum exposure are limited. However, extensive researches on every aspect of aluminum toxicity for the last 35 years proved that the metal should not be taken as safe. In spite of persistent arguments, it is well accepted that aluminum is a potent neurotoxicant. The risk is more at the perinatal age, because of more vulnerability of neuronal tissues. Thus, in this review, the available reports on perinatal aluminum toxicity are accumulated and an imperative aspect of aluminum toxicity is discussed as — why aluminum should be regarded as significant toxicant at perinatal age group, how perinates are exposed to aluminum, distribution of aluminum between the pregnant or lactating mother and prenatal or postnatal age groups, impairment of overall growth or development, alteration in other important trace elements and finally the impact on the neurobehavioral development with special emphasis.

SEVERITY OF ALUMINUM AS PERINATAL TOXICANT

Potentially noxious substances may act as fetal teratogens at levels far lower than those required producing detectable effects in adults; further, behavioural teratogenicity may occur at levels lower than those which produce morphological teratogenesis. Aluminum is a potential neurotoxin in adults and it is well accepted that it is capable of inducing neurobehavioral deficit even without altering the morphology. Due to lower bioavailability, the reproductive toxicity of aluminum is rarely assessed ([1]). Only in 1990s, aluminum is paid attention on its reproductive toxicity and it took nearly end of the last century to concern about embryo/fetal consequences of aluminum ingestion. Since pregnant women may be exposed to untoward levels of aluminum compounds under certain conditions ([2]), therefore aluminum toxicity may be of particular concern to the developing fetus. Very few studies on humans are available in this regard. However, a number of studies on animal model are presenting conflicting observations ([3]).

At the perinatal age, aluminum is highly neurotoxic ([4]) and inhibits prenatal and postnatal brain development ([5]). In addition, maternal dietary exposure to excess aluminum during gestation and lactation which did not produce maternal toxicity would be capable of causing permanent neurobehavioral deficits in weanling mice and rats ([6]). Over and above of these facts, the route and chemical form of aluminum exposure are two important determinants of the impacts of aluminum at this crucial age of neurodevelopment. It is well known that aluminum is a developmental toxicant specifically when administered parenterally. Although no evidence of maternal and embryo/fetal toxicity was observed when high doses of aluminum hydroxide were given orally to pregnant rats and mice during organogenesis; signs of maternal and developmental toxicity were found in mice when aluminum hydroxide was given concurrently with citric or lactic acids ([6]). So the future of life is being worsened even before birth, adding up the impact throughout life. However, the impacts are dependent upon the time of exposure, duration of exposure, route of exposure as well as form of exposure. As a result, the number of children in clinical populations that are at risk of aluminum toxicity is not known and needs to be determined.

INEVITABLE EXPOSURE TO ALUMINUM

In the earth's crust, the most abundant metallic element is aluminum. Despite its ubiquity, evolution has not conferred essentiality or utility as far as known in biological systems ([7]). Aluminum was being considered as nontoxic, nonabsorbable and harmless element for long; as a result it has been exempted from testing for safety by the Food and Drug Administration (FDA) under a convoluted logic wherein it is classified as GRAS (Generally Regarded As Safe). It has never been tested by the FDA on its safety and

there are no restrictions whatever on the amount or use of aluminum. Therefore, the light weight, shiny metal is being used extensively in our contemporary life. Aluminum has only recently been considered a problem mineral. Though it is not very toxic in normal levels, neither has it been found to be essential (http://www.bodychem.co.uk/body_aliminum.html).

Because aluminum permeates our air, water, and soil, environmental exposure to aluminum in the present day life is inevitable ([7]). Small amounts of aluminum are present in our foods, besides, food additives, foils and cooking utensils of aluminum-make are adding further aluminum to it. The concentration of aluminum in natural waters can vary significantly depending on various physicochemical and mineralogical factors. Aluminum levels in drinking-water vary according to the levels found in the source water and whether aluminum is used during water treatment ([8]). Aluminum salts are widely used in water treatment as coagulants to reduce organic matter, color, turbidity, and microorganism levels. Such use may lead to increased concentrations of aluminum in finished water ([9]). Iatrogenic exposure to aluminum is also adding to the increasing body aluminum burden ([7]). Moreover, children may ingest aluminum from dirt from unwashed hands or when playing in contaminated soils, vitamin/mineral supplements, and from consumer products not normally ingested by adults (e.g., toothpaste) ([6] , [10]). Dust from talcum powder, baby powder, cement, asphalt mixes, tobacco smoke and ashes contain aluminosilicates ([11]), thus may be of high concern of passive exposure to aluminum (Table I).

Figure 1

Table 1: Additional sources of aluminum at the perinatal age

Types	Common source of aluminum for both adult and infants	Additional source of aluminum in infancy
Iatrogenic	Over-the-counter drugs antacids, painkiller, anti-inflammatory drugs, douche preparations, etc. High aluminum-dialysate Aluminum-containing phosphate binders Parenteral solutions Alum Aluminum-containing bone cement Dental amalgams	Adjuvants in vaccines
Environmental	Air, Water	Soil (direct)
Consumables	Body spray, Body powder, Deodorants	Tooth paste Baby powder
Dietary	Food grains and vegetables Food additives Cooking utensils Drinks (Tea, Canned soft drinks)	Maternal milk Auxiliary nutrients Soya based milk Mineral supplements Vitamin supplements

Thus, exposure to aluminum is obligatory in the modern life. The irony is that the relative exposure load (in comparison to normal) is higher in the early life when the susceptibility is high ([12]).

TISSUE LEVEL OF ALUMINUM

In the perinatal period, mother is the prime source of aluminum exposure. Work in animal models (rats, mice, and rabbits) demonstrates that aluminum is distributed transplacentally and is present in milk ([6]).

Upon oral exposure to aluminum lactate during the day 0-19 of gestation causes significantly higher levels of aluminum in plasma, liver, spleen and kidneys of pregnant rats when compared to non-pregnant female rats ([13]). Cutaneous exposure of aluminum chloride throughout the gestation in mice led to an increase of aluminum in maternal serum, organs and amniotic fluid ([14]). Placental levels were increased in some studies as well, and were greater than corresponding fetal levels ([15]). However, Golub et al ([16]) did not found accumulation of aluminum in the guinea pig placenta. Studies with exposure to aluminum hydroxide, aluminum chloride, aluminum lactate or aluminum citrate during the gestation period showed that maternal aluminum levels were increased in some studies, but there was no consistent pattern of organ-specific accumulation.

Aluminum levels were found high in fetal serum and organs after cutaneous exposure to pregnant mothers ([14]). However, Muller et al ([13]) did not observed any difference in aluminum content of 20 days old fetuses of aluminum exposed mother and control mother. It is reported that upon subcutaneous injection of ^{26}Al into pregnant rats and/or lactating rats; aluminum was incorporated into the brain and nuclear fraction (brain cell nuclei) of fetuses and sucklings through the transplacental passage and/or maternal milk ([17]). Aluminum concentrations in the brain regions were highest in spinal cord, brainstem, and cerebellum, and found to be decreased during late gestation and lactation ([16]).

Muller et al ([18]) observed higher level of aluminum in milk one day after the aluminum treatment. Using ^{26}Al as a tracer, Yumoto et al ([19]) showed the incorporation of aluminum into the brain of sucklings through maternal milk. They have shown that the level of aluminum increased significantly in the cerebrum, cerebellum, spinal cord, liver and kidneys of suckling rats, though findings of Muller et al ([18]) did not corroborate these results. However, after weaning, the amounts of ^{26}Al decreased remarkably in the liver and

kidneys, while as much as 12-20% of the ^{26}Al present on day 20 postpartum remained in the cerebrum, cerebellum and spinal cord on day 730 postpartum. Thus they have concluded that considerable amounts of aluminum taken up into the brain of suckling rats through maternal milk remained in their brain throughout their lifetime ([19]).

Through studies with exclusively breastfed infants, Okolo et al ([20]) inferred that infants are able to extract aluminum from the breast milk. The situation becomes worse when the prematurity and/or renal failure is there. These reports, though sometime contradictory and inconclusive, suggest that aluminum entry via transplacental route or maternal milk can increase the lifetime burden of aluminum, especially in the brain.

WEIGHT GAIN OR GROWTH

Oral aluminum administration during pregnancy, at doses that also lead to reduced maternal weight gain, produces a syndrome including growth retardation, delayed ossification, and malformations in perinates ([6]). Gonda and Lehotzky ([21]) have reported that subcutaneous injection of aluminum on gestational days 7-15 does not have any effect on either the litter size or the body weight of pups in rats. On the other hand, Misawa and Shigeta ([22]) showed that the body weight of treated offspring can differ from that of control rats even if the mothers were treated with single dose of aluminum chloride. However, gestational exposure of aluminum found to significantly lower the postnatal body weight gain in rats ([21]). Prenatal exposure to intraperitoneal injection with aluminum sulfate during the days 10-13 exhibited decreased growth in treated pups in CBA mice ([23]). Similarly, exposure to aluminum lactate to pregnant Swiss mice ([24]) and aluminum hydroxide to pregnant Sprague-Dawley rats ([25]) during the gestational days 6-15 was found to reduce the fetal body weight significantly. In the contrary, Muller et al ([26]) did not found any effect of aluminum lactate treatment on the weight gain of pups. In addition to these, exposure of rats to aluminum nitrate by gavage from the 6th to 14th day resulted in decreased fetal body weight and increased the incidence and types of external, visceral, and skeletal malformations and variations in all the treated groups ([27]). Domingo et al ([28]) also showed that the growth of the offspring was significantly less from birth and during all the period of lactation for the higher doses of aluminum nitrate in an experiment with pregnant Sprague Dawley rats exposed to aluminum nitrate from the 14th day of gestation through 21 days of lactation. Lin et al ([29]) observed a dose dependent relationship between aluminum intake and intra-uterine growth retardation in mice and suggested that excessive aluminum ingestion during pregnancy may be a contributing factor to perinatal deaths. A reduction in average body weight was observed following postnatal (days 5 to 14) aluminum treatment and suggested that it could be due to decreased food consumption, transient undernutrition or reduced protein synthesis in liver ([30]). Therefore, these reports indicating that aluminum has a definite detrimental effect on the body weight gain in both fetuses and neonates. However, the extent of effects may vary according to the chemical form and route of exposure of aluminum.

ALTERATION IN TRACE ELEMENTS

High maternal intake of aluminum can result in altered essential trace element metabolism in the offspring ([31]). Belles et al ([32]) reported that oral aluminum exposure during pregnancy can produce significant changes in the tissue distribution of a number of essential elements. This is also observed by Muller et al ([13]) in both different tissue and plasma. In addition, calcium and magnesium levels in the whole fetuses from treated or nontreated dams are significantly different ([13]). High dietary aluminum can result in lowered tissue manganese and iron concentrations in weanling mice. Further study suggests that high dietary aluminum during development alters the ability of nursing mouse pups to retain absorbed iron and manganese ([33]). Thus, by altering the levels of necessary trace elements, aluminum may induce developmental deficits, which would be an added menace regarding aluminum toxicity. It is further supported by the observation that lumbar spine bone mineral density is negatively correlated with serum aluminum level in healthy premature infants ([34]). However, all the available reports are based on animal studies, so further study is needed to confirm the aluminum-induced alteration in trace elements and its impacts on the development, especially at the perinatal age.

DEVELOPMENTAL TOXICITY

Perinatal brain development is being inhibited by aluminum exposure ([5]). Experimental teratological studies revealed that over-intake of aluminum could lead obvious teratogenic and toxic effects on fetal development in mice. Effects of oral administration of different doses of aluminum during pregnancy on intra uterine fetal development in mice suggests that excessive ingestion of aluminum may be one of the risk factors contributing to congenital neural tube defects ([29]). Teratogenicity of aluminum was clearly identified after per os or iv administration ([14]). Rankin et al ([1])

demonstrated behavioral and neurochemical alterations in the offspring of mice exposed to aluminum during gestation and suggested the persistence of these behavioral deficits in adulthood. Alleva et al ([35]) reviewed the neurobehavioral alteration in rodents following developmental exposure to aluminum. According to them, the presented data showed behavioral and neurochemical changes in the offspring of aluminum-exposed mouse dams during gestation, which include alterations in the pattern of ultrasonic vocalizations and a marked reduction in central nervous system choline acetyltransferase activity. Prenatal aluminum also affects central nervous system cholinergic functions under nerve growth factor (NGF) control, as shown by increased central NGF levels and impaired performances in a maze learning task in young-adult mice ([35]). The neuromotor maturation of surviving pups from the mothers treated with the aluminum chloride and aluminum lactate throughout the gestation showed an important impairment during the first two weeks of postnatal life ([36]). On the other hand, Gomez et al ([37]) reported that even at gavage dose of 768mg/kg/day (equivalent to a 60kg person ingesting 16g aluminum/day) of aluminum hydroxide exposure from 6th to 15th day of gestation cannot cause any significant developmental toxicity in the fetuses. However, prenatal aluminum exposure resulted in a reduction in the rate of ultrasonic calling by pups accompanied by a shift in the timing of peak calling; and delays in neurobehavioral development ([23]). Findings of Gonda et al ([4]) also confirmed that postnatal behavioral effects can be induced in offspring prenatally exposed to aluminum lactate. The treatment received by a pup's foster mother was also found to influence development ([23]). Subcutaneous exposure of aluminum lactate on 7-15 gestational days in rats had no effect on the acquisition of a conditioned taste aversion, but in a passive avoidance task the learning ability of pups of dams given the top dose (9.8mg / kg) of aluminum was impaired ([21]). Then again, single exposure to aluminum chloride through gavage on the day 15 of gestation was found to alter the pinna detachment, eye opening, appearances of auditory startle and learning acquisition in THA rats ([22]). Thus, it has been suggested that single dose of aluminum chloride during prenatal period may affects the development and behavior in rats, while repeated exposure with lower doses of aluminum during the prenatal period found to affect neuromotor maturation and emotionality ([38]).

In the postnatal period, reduced pup weight gain and effects on neuromotor development have been described as a result of developmental exposures ([6]). Learning and memory changes were not observed after aluminum treatment of neonatal and immature rabbits ([39]). Whereas, the study of Golub et al ([40]) demonstrated aluminum-induced neurotoxicity in mouse dams and developmental retardation in their offspring following oral exposure to several dose levels during gestation and lactation. Observations of Kim ([41]) suggest that aluminum toxicity may be mediated through disturbances to the nitric oxide signaling pathway and exhibits a biphasic effect, especially in the frontal area of the cortex. It has been also suggested that impaired expression of neuronal nitric oxide synthase (nNOS) plays an important role in the development of neurological syndrome caused by an exposure to aluminum during the early developmental stage ([41]). Study with primary cultures of cerebellar neurons also suggested that prenatal exposure to aluminum significantly reduced the content of NOS and guanylate cyclase and increased the calmodulin content ([42]).

From the detailed study with excitatory postsynaptic potential, long term potentiation, long term depression and population spike in the rat dentate gyrus, Wang et al ([43]) concluded that the lactational period is the most susceptible to aluminum-induced impairment of synaptic plasticity and that chronic aluminum exposure from parturition throughout life is extremely disruptive to synaptic plasticity and should be avoided. Ravi et al ([44]) documented the long-term consequences of aluminum chloride exposure through gastric intubation in eight days old Wistar rat pups in terms of biogenic amine neurotransmitter in rat brain. Region specific alterations in the levels of adrenaline, serotonin, dopamine as well as acetylcholinesterase activity were found in response to postnatal aluminum exposure ([44]).

While experimenting with SPRD rat pups treated prenatlly with aluminum lactate to find out whether observational conditioning (social learning) could reverse the behavioral teratogenicity following aluminum treatment, Gonda et al ([45]) suggested that additional factors are involved in the effects of prenatal aluminum intoxication on cognitive processes. Studying with ‘realistic' diet, Golub and Germann ([5]) showed that developmental aluminum exposure under normal, but less than optimal, dietary conditions can lead to subtle but long-term effects on growth and brain function in adulthood. Lin et al ([29]) observed that aluminum could cause formation of encephalocele and dysostosis with an obvious dose-dependent relation. Immunohistochemical labeling study of the neurofilament protein of the highest molecular weight (NF-H) showed a delay in expression of phosphorylated NF-H in the pups of mothers those received

aluminum during gestation and lactation ([46]). However, authors have suggested that cause of this neurodevelopmental delay depends on multisystem defect and altered maternal homeostasis which cause variation in the aluminum delivery to the neonates ([46]). While studying the coexposure of aluminum and maternal restraints Colomina et al ([24]) suggest that maternal restraint could enhance the metal-induced developmental toxicity (reduced fetal body weight, increase in the number of litters with morphologic defects) only at high doses of the metal, which are also toxic to the dam.

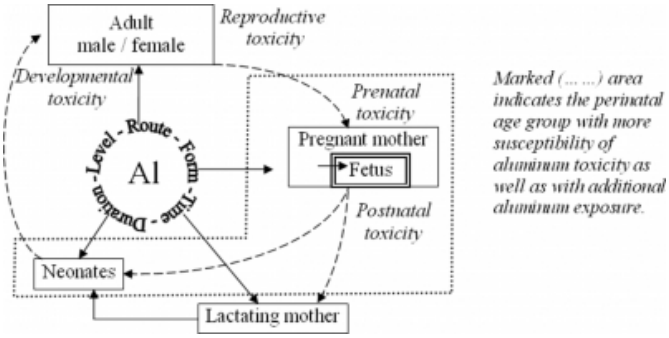
The significance of these findings for human health requires better understanding of the amount and bioavailability of aluminum in food, drinking water, and medications as well as sources unique to infants and children such as breast milk, soil ingestion, and medications used specifically by pregnant women and children ([6]). In preterm infants, Bishops et al ([47]) found that prolonged intravenous feeding with solutions containing aluminum is associated with impaired neurologic development.

SUMMARY

The so-called ‘non-toxic' metal aluminum is already well accepted as neurotoxin, however, the argument about the role of aluminum in different neuropathology is continued without a firm conclusion of whether the metal is itself a causative agent or just being accumulated to worsen the pathological consequences. Whatever may be the situation, certain neuropathologies are well associated with the accumulation of aluminum. Again, number of factors, including exposure level, form of aluminum, route of exposure, accompanying chemicals, etc. are determining the accumulation level of metal and in turn the pathological consequences (Figure I). The dominance of higher susceptibility to aluminum toxicity, especially at perinatal age, over other determinants, is highlighted by the findings cited here. Elevated aluminum exposure level at this vulnerable age might produce a lifelong toxicological consequence.

Figure 2

Figure 1: Interrelated exposure and susceptibility of aluminum in the perinatal age group.



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