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Review

Aluminum in vaccines: Does it create a safety problem?

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ABSTRACT

For almost a century, aluminum (Al) in the form of Al oxyhydroxide (a crystalline compound), Al hydroxyphosphate (an amorphous Al phosphate hydroxide), Al phosphate, and Al potassium sulfate has been used to improve the immunogenicity of vaccines. Al is currently included in vaccines against tetanus, hepatitis A, hepatitis B, human papillomavirus, *Haemophilus influenzae* type b, and infections due to *Streptococcus pneumoniae* and *Neisseria meningitidis*. Official health authorities consider the inclusion of Al in most of the presently recommended vaccines to be extremely effective and sufficiently safe. However, the inclusion of Al salts in vaccines has been debated for several years because of studies that seem to indicate that chronic Al exposure through vaccine administration can interfere with cellular and metabolic processes leading to severe neurologic diseases. Children, who in their first years of life receive several vaccine doses over a reduced period of time, would be most susceptible to any risk that might be associated with vaccines or vaccine components. The main aim of this paper was to discuss the data presently available regarding Al neurotoxicity and the risk for children receiving vaccines or other pharmaceutical preparations containing Al. Analysis of the literature showed that no apparent reason exists to support the elimination of Al from vaccines for fear of neurotoxicity. The only problem that deserves attention is the suggested relationship between Al oxyhydroxide-containing vaccines and macrophagic myofaciitis or myalgic encephalomyelitis/chronic fatigue syndrome. Currently, definitive conclusions cannot be drawn on these risks and further studies must be conducted. Until then, Al remains the best solution to improve vaccine efficacy.

Contents

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1. Introduction

For almost a century, aluminum (Al) in the form of Al oxyhydroxide (a crystalline compound), Al hydroxyphosphate (an amorphous Al phosphate hydroxide), Al phosphate, and Al potassium sulfate has been used to improve the immunogenicity of vaccines [1]. Al is currently included in vaccines against tetanus, hepatitis A, hepatitis B, human papillomavirus, *Haemophilus influenzae* type b, and infections due to *Streptococcus pneumoniae* and *Neisseria meningitidis*. Official health authorities consider the inclusion of Al in most of the presently recommended vaccines to be extremely effective and sufficiently safe. In a workshop sponsored by the US National Vaccine Program Office, which was specifically planned to discuss the role of Al in vaccines, invited international experts concluded that Al salts were capable of directly stimulating the immune system through the activation of antigen-presenting cells, complement cascades, and the induction of chemokine secretion [1]. Consequently, when added to vaccine antigens, Al can lead to a significant increase in the immune response with higher and more persistent production of specific antibodies against antigens included in the vaccines, although its largest flaw is that Al usually only induces a Th2 immune response. Moreover, the same workshop demonstrated that Al adjuvants have an apparent wide margin of safety because adverse events following their administration were uncommon and showed poor clinical relevance. Although these and similar statements are shared by scientific authorities worldwide [2,3], the inclusion of Al salts in vaccines has been debated for several years, and it is one of the problems that might partially explain the vaccine refusals of some parents and physicians [4]. Studies that seem to indicate that chronic Al exposure through vaccine administration can interfere with several cellular and metabolic processes leading to severe diseases, including neurodevelopmental delay, autism spectrum disorder (ASD) and Alzheimer's disease (AD), are the basis for this debate [5–10].

Children, who in their first years of life receive several vaccine doses over a reduced period of time, are considered to be at the highest risk for Al-dependent, vaccine-related complications. Despite reassurances from health authorities, the question continues to be raised, and the elimination of Al from vaccines continues to be discussed, even through the mass media [11]. Recently, a study showing that subcutaneous injections of Al at vaccine-adjuvant levels activated homologous genes with biomarkers of autism in mouse brains has provided even more support for the opponents of vaccines. Practically, some supposed that this study might represent the final demonstration that Al induces the development of autism in predisposed individuals. The article was retracted a few weeks after its publication at the request of the editor-in-chief and the authors because the data and the results presented in the paper were clearly not reliable [12]. However, as has previously occurred for the supposed relationship between the measles, mumps and rubella vaccine and autism [13], negative data can have a greater resonance than their retraction, and the risk that fake news persistently supports vaccine opponents remains significant. The main aim of this paper was to discuss the data presently available regarding Al neurotoxicity and the risk for children receiving vaccines or other pharmaceutical preparations containing Al.

2. Aluminum (AL) disposition

Al is an environmental metal that is the third most abundant element in the earth's crust and represents approximately 8% of the crust's total mineral components. Moreover, it is largely used in many human activities, including food and drug preparation. Finally, the release of Al to the air from industrial processes and acidic precipitation, which mobilizes the metal from natural sources, is common [14]. This airborne Al can pass to the water or be inhaled. Thus, humans are continuously exposed to Al, and it can be found (although in different concentrations) in all of the body tissues and fluids beginning at birth. Starting with the evidence that the mean Al blood level of term neonates is 0.19 ± 01 1 μmol/L [15] and that the Al in the blood accounts for approximately 4% of the total Al in the body [16], the total body content of this metal at birth has been calculated to be approximately 400 μg [17].

Total body Al concentrations increase with exposure and are generally significantly higher in adults than in children. The highest levels are found in the skeletal system and the lungs, which contain approximately 50% and 25% of the body burden, respectively. Significantly lower concentrations, 10%, 3% and 1%, are usually detected in the muscle, liver and brain, respectively [18].

Food and vaccines are the most important sources of Al for infants and young children. However, vaccines play a major role in this regard because Al absorption from the gastrointestinal tract is poor. Approximately 0.2–0.4% of the ingested Al is absorbed and reaches the bloodstream, with variations based on the type of Al salt [19,20]. During infancy, general fluid consumption varies from approximately 600–900 mL per day, and Al intake depends on the dietary source. Breast milk contains a mean of 40 μg/L, whereas Al levels in formula are significantly higher, ranging from 225 μg/L to 1150 μg/L because food industries use Al components in processing facilities and add Al to food preparation to improve mixing and reduce caking [21–25]. After weaning, Al intake increases and reaches a mean of approximately 700 μg per day [26]. Thus, no more than 2–3 μg per day of Al derived from food enter the systemic circulation during the first year of life. In contrast, almost the full amount of Al included in vaccines given intramuscularly is bioavailable, albeit at a rate over time and with differences among Al salts [27]. It has been calculated that only 51% of Al phosphate and 17% of Al hydroxide reach the bloodstream after a single intramuscular (i.m.) injection in the first 28 days after injection, and the remaining amount is absorbed in 28 and 137 days, respectively [17]. In vaccines, the maximum amount of Al per dose varies from vaccine to vaccine, with a maximum in combined preparations that can range from slightly more than 800 μg per dose, a value that matches the US regulations that limit the amount of Al in the recommended individual dose of biological products (including vaccines), to not more than 850–1250 μg. An FDA study found that the maximum amount of Al an infant should be exposed to over the first year of life is 4225 μg when the recommended ACIP vaccine schedule is used for calculation. This finding was confirmed by Glanz et al., who examined the cumulative and episodic vaccine Al exposure in a sample of 408,608 children ranging in age from birth to 24 months [28]. The mean cumulative Al exposure from the vaccines varied from 1110 ± 320 μg to 4000 ± 800 μg between 92 and 730 days of age. In 2002, an attempt was made to evaluate whether intakes due to food and vaccines could be excessive and lead to clinical problems. Keith et al. compared the calculated body burdens with those expected for exposure at a level considered safe for intermediate-duration exposure according to the minimum risk level (MRL) established at that time (2000 μg/kg/day) by the Agency for Toxic Substances and Disease Registry [29]. These authors found that during the first year of life, the calculated body burden from Al exposure from food was always below the MRL curve, suggesting that diet could not cause clinical problems. The same findings were reported for vaccines for all but a few brief periods following injection. Recently, the analysis of Keith et al. was updated, and new parameters were included [29]. Contemporaneous MRLs (1000 μg/kg/day) and some variables capable of better evaluating the retention and excretion of Al in younger children were introduced [27]. In this study, previous data

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were substantially confirmed [27]. However, considering the speed with which Al is absorbed from the injection site, the body burden of Al from vaccines was only 2-fold higher than that of foods.

However, both of these studies were strongly criticized. In the opinion of Masson et al. [30], Keith et al. used too high of an MRL together with an erroneous model of 100% immediate absorption of vaccine Al [29]. Moreover, the authors did not consider renal or blood-brain barrier immaturity. Although significantly improved from a methodological point of view, the results of Mitkus et al. were also debated [17]. Once again, the MRL (1000 μg/kg/day), although lower than that used in the previous study, was considered too high compared with the amount used in experimental studies of Al-induced memory and behavioral changes. However, the most important criticism was that Mitkus et al. did not account for the elimination of Al from the body as being different when the element is ingested or inhaled or when it is injected via the intramuscular route [17]. When Al is ingested or inhaled, body accumulation occurs only when intake is abnormally high or when renal elimination is significantly impaired. In contrast, when Al is injected together with vaccine antigens, elimination is slower because a relevant portion of Al remains at the injection site inside the macrophages that initiate the immune response [31]. Phagocytes transport Al particles relatively quickly to the lymphoid organs and then to the bloodstream [32]. Cells with Al might reach distant organs.

3. The neurotoxicity of aluminum (AL)

3.1. Unquestionable demonstrations of aluminum (Al) neurotoxicity

Several *in vitro*, experimental and epidemiological studies have clearly shown that Al is toxic, especially for the central nervous system (CNS). It has been reported that Al in the brain significantly alters cellular functions, both through interference with energy metabolism and phosphorylation and dephosphorylation processes and through modification of gene expression. Moreover, it reduces neurotransmitter release, influences the activity of ion channels, alters membrane properties, and favours abnormal protein accumulation [33]. To avoid the risk of severe adverse events following Al exposure, many health authorities have defined maximum tolerable oral intakes. As previously reported, the US has defined the oral MRL as 1000 μg/kg/day for both acute and chronic administration [34]. However, the World Health Organization [35] and the European Food Safety Authority [36] have stated significantly lower values, indicating the provisional tolerable weekly intake as 2000 μg/kg and 1000 μg/kg, respectively. All of these reference values are based on oral intake and do not consider other routes of Al, including vaccine administration. Consequently, they have a limited value for identifying the real risk of exposure. To overcome this problem, urine and serum maximal tolerable concentrations have been established based on values found in healthy adults and those with true Al-related diseases. Al levels <15 μg/L in urine and <5 μg/L in serum are considered the background exposure levels of the general population. The early signs of neurotoxicity usually occur when Al levels are ≥13 μg/L in plasma and ≥120 μg/L in urine. Finally, the critical value for significant encephalopathy is 50 μg/L in plasma, whereas no definitive value has been established for urine [37–40]. However, reference values for children have not been defined. Consequently, it is very difficult to interpret serum and urine values in children, particularly the youngest [41]. On the other hand, information concerning the age-related toxicity of Al, particularly in young children, is very poor.

However, most of the cases in which a clear relationship exists between Al exposure and the development of neurotoxicity have been reported in animals and individuals with severe renal insufficiency or those exposed to high Al concentrations for months. Behavioral alterations have been demonstrated in rats when the animals were intraperitoneally (ip) injected for 6 months with 850 μg/kg three times per week [42]. Dramatic retinal changes were observed in rats injected ip with 0.3 mL of 4% $AlCl_3$ per day every day for 16 weeks [43]. A higher incidence of subjective neurological symptoms such as problems concentrating, depression, and fatigue were described in Al potroom or foundry workers at Al smelters who were exposed to very high inhaled Al doses and who had medium urine and serum concentrations that were well above the aforementioned reference values [44,45]. Impaired speech, apraxia and, later, dementia were found in patients with end-stage renal disease who were chronically dialysed with solutions containing Al or who continuously used gastric antacids or Al phosphate binders. In these cases, plasma Al concentrations between 80 and 500 μg/L were observed. Moreover, specific EEG changes (alternating spikes and slow waves) that are considered characteristic of Al toxicity were shown. However, brain tissue modifications were minimal (slight cellular loss in the cortex, hippocampus and Purkinje cells) [40,46–50]. The accumulation of Al with the development of impaired bone mineralization and delayed neurological development was also observed in premature children with a physiologically reduced glomerular filtration rate who received long-term parenteral nutrition with a solution with a high Al content [51].

3.2. Potential association between aluminum (Al) and Alzheimer's disease and autism spectrum disorder (ASD): pros and cons

A potential association has been supposed between chronic Al exposure and the development of AD or ASD based on specific histochemical findings and epidemiological studies. Some studies have found that Al administration was followed by the development of brain lesions in animals, similar to those observed in people with AD [52]. However, the doses used in these experimental studies were abnormally high and far from those to which normal people are exposed. Moreover, the hypothesis that the accumulation of amyloid beta protein and amyloid plaque associated with AD was because Al use has largely waned given the numerous studies that have not found higher Al concentrations in the brains of patients with AD than in the brains of age- and sex-matched controls [53–56]. On the other hand, the histologic brain lesions shown in patients with dialysis-associated neurotoxicity were quite different from those typically reported in people with AD [40]. Furthermore, most of the data collected from epidemiological studies reject the hypothesis of an association between Al and AD development. Rondeau et al. reported that a high daily intake of Al through water was associated with cognitive impairment or AD [57]. This finding seems to suggest that Al is neurotoxic and that a real correlation exists between Al and AD. Moreover, neither Virk et al. [58] nor Salib et al. [59] found differences in the incidence of AD between individuals with chronic environmental Al exposure and controls. In contrast, Wang et al. reported apparently positive results [60]. These authors analysed 8 cohort and case-control studies involving 10 587 individuals and found that participants with chronic Al exposure through food or inhalation had a higher risk for AD development (odds ratio [OR] 1.71, 95% confidence interval [CI] 1.35–2.18). However, the results of this study were debated primarily because the study included participants without a definitive diagnosis of AD; therefore, it was possible that numerous dementia cases of different origins were included. Also debatable are the conclusions of Walton [61], who applied Hill's causality criteria to establish causality between exposure and outcome using the available data reporting that Al plays a causative role in the development of AD. A correlation was not definitively

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demonstrated, but even if it had been, this finding could not be considered evidence of causation. However, no relationship was demonstrated between Al-containing vaccines and AD.

Similar limitations are characteristic of the studies regarding AD, particularly those studying the parenteral administration of Al, as occurs in vaccines. The results of studies in experimental animals cannot be generalized to humans because of the differences in administered Al doses and the methods used for administration. For example, in the animal model developed to explore the potential behavioral phenotypes and CNS alterations in early postnatal mice, Al was injected subcutaneously instead of i.m. as routinely occurs in children when vaccines with Al are given [62]. Tomljenovic and Shaw found that the increase in exposure to Al adjuvants was significantly correlated with the increase in ASD prevalence in the USA ($r = 0.92$, $p < 0.0001$) [63]. Moreover, the amount of Al administered at 3–4 months of age is correlated with the current prevalence of ASD in seven Western countries ($r = 0.89–0.94$, $p = 0.0018–0.0248$). These findings led the authors to conclude that Al is a potential contributing factor in the development of AD. However, this study has some problems. First, correlation and causation were confused. Moreover, as the Global Advisory Committee on Vaccine Safety stated [2], this and another study on the same topic by the same authors were seriously flawed [64]. Importantly, ecological studies, such as those carried out by these authors, cannot be used to assert a causal association because they do not link exposure to outcomes in individuals, and only make correlations between exposure and outcomes on population averages. Moreover, these studies were characterized by inaccurate ASD rates across different countries and differences in vaccination schedule among countries. On the other hand, a recent study that evaluated blood and hair Al levels, vaccine history and early infant development failed to demonstrate any correlation between Al blood levels and different aspects of infant development [65]. Similar findings were reported for hair concentrations, although an inverse relationship was found when motor scores were studied. However, extreme outlier hair Al values that might have decreased the significance of the results were excluded from the calculation, thereby limiting the value of this finding.

3.3. The problem of aluminum (Al) adjuvants and the development of macrophagic myofaciitis (MMF) and the autoimmune/autoinflammatory syndrome (ASIA) induced by adjuvants

To increase the evidence that use of Al-containing pharmaceutical preparations lead to brain damage, supporters of this hypothesis have attempted to link immunization and the administration of Al-containing allergens for immunotherapy with the development of the autoimmune/autoinflammatory syndrome induced by adjuvants (ASIA) and, in particular, with macrophagic myofaciitis (MMF). ASIA was first described in 2011 and was defined as a group of disorders including autoimmunity, sick building syndrome, silicosis, Gulf war syndrome and macrophagic myofaciitis (MMF) occurring in individuals who have been exposed to vaccine adjuvants, including Al oxyhydroxide, or to various chemicals [66,67]. Moreover, it was recently suggested that lymphoma, Sjogren syndrome, narcolepsy, and phospholipid syndrome can be included in ASIA and possibly related to adjuvant administration [68–70]. Most of the data regarding the potential association between Al and the development of autoimmune diseases included in ASIA have been collected amongst patients who have received the hepatitis B and human papillomavirus vaccines [67]. Until now, more than 4000 cases have been reported [71]. However, most of the data that seem to identify vaccines as the cause of ASIA are unconvincing. First, the described cases of ASIA have been diagnosed using criteria that are not specific. The diagnostic criteria suggested by Sheonfeld and Agmon-Levin include conditions that are commonly experienced in the community [72]. For example, the major criteria include exposure to either a vaccine adjuvant or an infection, a condition that occurs several times in any individual's life. Moreover, the long list of "typical" manifestations include myalgia, fatigue, pyrexia and insomnia; all of these symptoms commonly occur in a multitude of participants without autoimmunity. Furthermore, the major criteria leading to diagnoses of autoimmune disease and chronic fatigue syndrome practically leads to the diagnosis of ASIA in all cases. It is highly likely that all patients with an autoimmune disease or chronic fatigue syndrome have had a fever during the same period of time. Finally, most patients with autoimmunity have HLA haplotypes considered particular to ASIA. In addition, given the numerous participants who qualify for this diagnosis in this case, it is reasonable to raise questions about the specificity of this criterion [73]. Moreover, a large data series from human studies seem to negate the correlation between Al administration and any ASIA clinical manifestation. One year after the description of ASIA, an analysis of the available data led to the conclusion that the evidence that intradermal immunotherapy with Al-containing preparations can induce autoimmune diseases was very weak and was supported only by anecdote [74]. More recently, no association was found either between the hepatitis B vaccine and *Haemophilus influenzae* type b vaccine or between the hepatitis B vaccine and the development of multiple sclerosis or type 1 diabetes [75]. In addition (and contrary to what might be expected if Al-containing vaccines were capable of inducing autoimmunity), no increase in exacerbations in patients suffering from systemic lupus erythematosus who had received hepatitis B vaccine was reported [76]. Finally, the incidence of autoimmune diseases was lower in patients with allergic rhinitis treated with Al-containing antigen preparations than in those treated with nasal spray and antihistamines [74]. A recent study of 18,841 patients receiving an allergen-specific immunotherapy were compared with 428,484 conventionally treated participants confirmed this finding [73]. Interestingly, this study calculated no increase in autoimmune diseases, even though patients receiving allergen-specific immunotherapy had received 100–500 times more Al over 3–5 years than those given the hepatitis B or human papillomavirus vaccines.

Additional interesting data have been collected regarding MMF. This condition is characterized by a muscular lesion at the site of a previous i.m. vaccination in which large macrophages frequently containing Al oxyhydroxide and lymphocytes are included [77]. Muscle lesions are systematically associated with systemic signs and symptoms of diseases such as diffuse myalgias, chronic fatigue, and cognitive impairment. Taken together, these findings constitute the so-called myalgic encephalomyelitis/chronic fatigue syndrome (ME/CFS) that is diagnosed in approximately 50% of all patients with MMF [78,79]. Because no exposure to Al other than that due to vaccines was detected, immunization was considered the possible cause of the disease. However, this disease is rare and is diagnosed primarily in adults months or years after vaccine administration, most likely depending on inter-patient variation in the clearance of Al oxyhydroxide. A few sporadic paediatric cases have been described, and the association between MMF and CNS involvement is unclear in this population [80–84]. Al oxyhydroxide is the Al salt commonly found, although other Al salts are also included in vaccines, because Al oxyhydroxide has a much longer tissue residence time than other Al salts, which causes more persistent muscle lesions in experimental animals similar to those found in patients with MMF [85]. As previous reported, Al oxyhydroxide might affect immune cells in the brain and cause damage. To explain why billions of doses of vaccines containing Al oxyhydroxide did not cause any relevant problems and why MMF with brain damage occurs in very few cases, it was suggested that certain genetic characteristics of individuals play a role in this regard.

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Some cases of MMF have been diagnosed in patients of the HLA-DRB1*01 group, which is associated with an increased risk of developing autoimmune diseases [86]. Moreover, other genetic factors can favour the brain penetration of Al. Studies involving experimental animals have demonstrated that Al translocation is higher after a systemic or cerebral increase in the activity of monocyte chemoattractant protein-1 (MCP-1/CCL2). This chemokine plays a fundamental role in the regulation of the migration and infiltration of monocytes/macrophages and can influence Al biodistribution [87]. Elevated levels were found in the sera of patients with MMF [88]. Because MCP-1/CCL2 expression varies by age as well as genetic and environmental factors, it was considered plausible that the Al oxyhydroxide included in vaccines causes MMF and brain damage in predisposed patients [8].

Interestingly, the finding that the genotyping for 4 single nucleotide polymorphisms (SNPs) localized in the CCL2 gene of patients with MMF (but not controls) showed that the AG haplotype of the SNP rs3760396C was associated with a slightly increased risk for disease [32]. However, despite these intriguing findings, the direct relationship between the Al oxyhydroxide contained in vaccines and the brain damage accompanying some cases of MMF should not be considered fully demonstrated. MMF unrelated to vaccination has been described, which suggests that other causes unrelated to vaccination are the cause of this clinical problem [89].

4. Conclusions

Presently, no population-based studies regarding the potential association between the Al in vaccines and the development of neurotoxicity have been conducted. This limits the evaluation of the neurotoxicity of Al-containing vaccines. However, billions of doses of these prophylactic preparations have been administered to children without incident and with enormous advantages regarding the prevention of common and severe infectious diseases. However, exposure to Al is associated with the development of severe clinical problems, including CNS deterioration. Fortunately, certain associations were found only in cases of long-term exposure to high amounts of Al or when the renal excretion of the element was impaired due to severe renal insufficiency. Moreover, the development of AD after Al exposure is far from certain, as is the potential correlation between Al-containing vaccines and ASIA. Although the bioavailability of Al included in vaccines differs from that of the Al derived from water, food or inhalation, and the exposure of young children to Al from vaccines is not precisely defined, the total Al exposure from immunization is likely significantly lower than the level that causes neurotoxicity. Furthermore, studies that seem to demonstrate a possible correlation between vaccines and ADS development in children are strongly debated because they are seriously flawed. Thus, current data do not support the elimination of Al from vaccines for fear of neurotoxicity.

The problem that deserves attention is the suggested relationship between Al oxyhydroxide -containing vaccines and MMF or ME/CSF. This relationship is supported by a series of experimental findings and specific data collected from patients that suggest that, in some cases, the Al contained in macrophages at the site of injection can reach the brain and cause damage in a few individuals who most likely have a genetic predisposition. Importantly, the described cases of MMF and ME/CSF are very few, and MMF cases not related to adjuvants have been described. Currently, definitive conclusions cannot be drawn. Thus, several studies must be conducted. Until then, Al improves vaccine immunogenicity and performance, and should be maintained; nevertheless, research on the pharmacokinetics of Al in vaccines should be encouraged.

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Conflicts of interest

None to declare.

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