REVIEW ARTICLE

Aluminum Adjuvant in Vaccines: A New Research Avenue is Demanded

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Abstract

Background: For nearly a century, aluminum hydroxide (alum) has continued to be employed as an adjuvant in vaccinations. It was first applied by immunologist Alexander T. Glenny in 1926 to boost the immune response. Its great efficiency has allowed aluminum to continue to be used to date.
Methods: Recognized scientific databases such as Google Scholar, Web of Science, and PubMed were utilized to search for the keywords. The selected works were reviewed and analyzed according to their relevance. Only peer-reviewed articles were included in the analysis.
Results: Contemporary research carried out on animals has shown that it has a neurotoxic effect. Furthermore, increased aluminum concentrations in the nervous system tissues of people, who died from an autism condition have been discovered by using advanced imaging techniques. The paradigm shift proposes a reconsideration of the use of the alum-based adjuvants and calls for a careful dissection to avoid incorrect interpretations. This proposal does not constitute an attack on vaccination, as nobody refutes the fact that it has been systematically proven to be effective in saving millions of lives. Unfortunately, scientists, who have investigated the toxicity of aluminum-based adjuvants have been unfairly labeled as "anti-vaxxers". Rather, what they have been questioning is the safety of aluminum as an adjuvant.
Conclusions: The present work encourages researchers, health regulatory agencies, and even pharmaceutical companies to allow themselves to think about the possibility that aluminum-based adjuvants could be toxic for susceptible children.

Keywords: Autism, Neurotoxicity, Vaccination, Paradigm Shift

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INTRODUCTION

From the time when the first vaccine was developed and approved [1], vaccination achieves undisputable success by offering protection against various virulent infectious diseases. This exceptional position of the vaccine in the everyday life is supported by the information generated in many different fields of science. Immunization is the most efficient healthcare intervention developed, and when accompanied by sufficient hygienic conditions and antibiotics, having removed a substantial proportion of the contagious illnesses that once provoked the loss of many lives [2]. Today, more than 25 virulent and deleterious infectious agents have a protective vaccine, and as a result, millions of people's lives have been saved by vaccination. Adjuvants have long been used to boost a vaccine's adaptive response, depending on antibody levels or disease-prevention capabilities, but they have recently taken a new role; directing the immune reaction to develop the best effective way of protection for each pathogen [3].

METHODS

Several well-known scientific databases, including Google Scholar, Scopus, and PubMed, were searched in order to find the referenced publications, which have been published throughout the past six decades. The terms "Autism", "Neurotoxicity", "Vaccination", and "Paradigm shift" were used as the keywords. Before composing the literature, selected contents were assessed at various stages, and the final version was approved by all the authors.

RESULTS

Adjuvare is a word that has been taken from Latin to explain how adjuvants work. It means "to assist" [4]. The immunostimulatory action of aluminum-containing adjuvants was described for the first time in 1926 by Alexander T. Glenny [5]. Aluminum, in addition to being a powerful immune system activator, is toxic for neurons and has been proven to affect brain growth before and after birth in our species and animals

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[6, 7]. Nevertheless, alum was and still is the most widely employed vaccine adjuvant for human vaccines [8], followed by calcium phosphate [9], and, in recent times, the MF59 adjuvant based on squalene [10]. Many national and international organizations have approved all of these vaccine adjuvants, but we will use the World Health Organization (WHO) as an acceptable and consensus source throughout this article. As stated below, multiple papers based on experimental assessments have linked the usage of aluminum salts as a vaccination adjuvant to neurological diseases for more than 55 years [11, 12, 13]. These issues may be the reason for many pharmaceutical companies' recent creation of nanoparticulated new alum and partial transition to calcium phosphate adjuvant; however, the aluminum is still present in vaccinations, though in the nanoparticle form [11,12,13].

Is a Paradigm Shift Necessary?

A paradigm is a set of preconceptions, attitudes, behavioral patterns, and activities that define a community's way of perceiving reality, particularly in an academic organization [14]. Researchers in science frequently look at "one side of the coin" owing to incapacity or reluctance to see outside of conventional thinking patterns [14]. This appears to be the situation with vaccine adjuvants. It is worth noting that scientists and health regulatory organizations have not looked for safer and more efficient adjuvants in over a century, and vaccine adjuvant development is acknowledged to be one of the slowest processes in medical history [15].

This is the most important feature of a paradigm: once it is accepted and adopted by the majority of scientists, it becomes the truth; no one doubts its validity, and no one dares to criticize it. The refusal to accept a new paradigm is common, and Thomas Kuhn captured it brilliantly in his book *The Structure of Scientific Revolutions* [14]. "Scientific revolutions are those noncumulative developmental experiences in which an older paradigm is partially or completely replaced by an incompatible new one," he stated. According to Kuhn, a scientific revolution arises when researchers find abnormalities that cannot be interpreted by the globally accepted paradigm that has guided scientific development thus far. Such abnormalities serve as the foundation for the development of a new paradigm [14].

Several scientists have discovered several "anomalies" in recent years that contradict the widely held belief that aluminum-based adjuvants are completely safe. As a result, the purpose of this paper is to show the latest scientific evidence demonstrating that, while aluminum is an effective adjuvant, it can be neurotoxic in susceptible people and may be associated with the emergence of illnesses such as autism spectrum disorders (ASD), Alzheimer, Parkinson, and multiple sclerosis [16].

The Accepted Paradigm

In general terms, the accepted paradigm in the field of the utilization of aluminum salts as safe adjuvants is based on three statements:

1. Only high quantities of aluminum in the body can be dangerous.

2. Dietary aluminum and aluminum from vaccines have the same chemical composition.

3. Aluminum from vaccines is easily eliminated from the body.

The following analysis of recent experimental evidence will demonstrate that these statements should be objectively re-evaluated.

1. Only High Quantities of Aluminum in the Body can be Dangerous

The well-known adage "the dose makes the poison", coined by Paracelsus, is the foundation of classical toxicology. This implies that several harmful compounds are safe in small amounts, but have evident toxic consequences when the dose is increased. According to this toxicological concept, it has been stated that, due to the absorption of aluminum from food sources, children are expected to consume far more aluminum via their meals than via immunizations. Following this approach, it is believed that aluminum from vaccination is not a toxicological risk factor because the amounts of aluminum used in vaccinations are not high enough to produce toxicity to neurons [17, 18]. This claim, on the other hand, is not substantiated by the latest evidence, and its validity should be re-evaluated.

In 2017, a group of scientists [19] assessed mouse cerebral activity and aluminum content 180 days following the injection of diverse concentrations of aluminum hydroxide (alum or Alhydrogel®) in a leg muscle in adult female CD1 mice (200µg, 400µg, and 800 µg of alum/kg). 8 validated procedures were used to assess cognitive and motor function, Iba-1 immunohistochemistry was employed to assess microglial activation, and graphite furnace atomic absorption spectroscopy was utilized to quantify aluminum levels [19]. It was discovered that an atypical neurotoxicological phenomenon was confined to a small concentration of Alhydrogel®. In mice treated with 200 µg Alum/kg but not 400µg or 800 µg Alum/kg, neurobehavioral alterations such as decreased levels of activity and anxious behavior were detected in comparison with the reference cohort. The number of microglial cells in the anterior part of the brain of the 200 µg Al/kg group appeared to be notably higher [19].

The analysis of brain aluminum concentrations revealed a significantly higher aluminum content ($p = 0.011$) in the brains of mice inoculated with 200 µg Alum/kg, but no substantial increase in the brains of mice inoculated with 400 µg or 800 µg Alum/kg. Because brain aluminum concentrations were not elevated in mice treated with 400µg or 800 µg Alum/kg, the absence of neurological toxic effects reported with these large concentrations was most likely due to restricted aluminum brain transfer (it is possible that tiny aluminum particles associated with the 200 µg dose can be ingested by macrophages and carried to the brain) (Trojan horse mechanism), while larger particles observed with greater Alhydrogel concentrations are unable to be carried to the brain and persist at the injection area [19].

Proof of a non-monotonic concentration reactivity graph for Alhydrogel neurotoxic ®'s effects, with the specificity of toxic effects with the smallest concentration employed in that

investigation, indicates that the dose does not always make the poison. To summarize, such non-linear dose-response pattern, wherein the smallest concentration but not the higher ones is toxic to mice´s neurons, is a breakthrough discovery in the area of aluminum adjuvant toxicity [19]. When nanoparticles achieve a certain size, they could display distinct features than non-nanoparticles and begin to exhibit deleterious effects, such as neuronal toxicity [20, 21].

Research has recently been undertaken to explore the probable relationship between AlNP (aluminum nanoparticles) administration and immune system modulation in vivo, as well as to explain the processes that underpin it. AlNPs were discovered to concentrate in the immunological organs of mice, producing oxidative injury and immune cell malfunction, likely contributing to the aberrant cytokine release, culminating in the negative consequences of AlNPs on the immunological system of these rodents [22]. In mice, AlNPs also promote necrotic cell death and apoptosis [23, 24].

2. Aluminum from Food and Aluminum from Vaccines have the Same Chemical Composition

Aluminum from vaccination is not thought to be a toxicological health risk, as previously stated, since "children acquire significantly more aluminum through nutrition than from immunizations" [17,18]. This statement is inaccurate as it fails to recognize the fundamental physicochemical distinctions between ionic aluminum (Al^{+3}) acquired from meals and aluminum hydroxide (Al (OH) 3) employed as a vaccine adjuvant.

In other words, unlike soluble diet aluminum, which reaches the bloodstream and is excreted by the kidneys, aluminum hydroxide adjuvant nanoparticles are practically non soluble at pH 7.35 and largely persist in the granular form [25]. As a result, aluminum toxicologists have realized that contrasting the toxicological features of distinct types of aluminum (soluble vs. insoluble) supplied via different pathways (orally vs. intramuscularly) is inadequate [26].

Soluble aluminum, such as that found in foods, cannot be utilized as an adjuvant since it needs to be in the undissolved state in order to allow adsorption to the antigen; thus, adjuvants containing aluminum are made creating a chemical precipitate of high pH aqueous solutions of aluminum ions [27]. Because the antigen-aluminum mixture is insoluble, it can't be efficiently excreted in urine or stools, as has been repeatedly stated. The underlying physicochemical distinction between dietary and vaccine-formulated aluminum should be acknowledged by scientists working for health regulatory agencies [26].

3. Aluminum from Vaccines is easily Eliminated from the Body

For a long time, expert international congresses claimed that aluminum given by vaccination route was practically quickly removed from the body via the kidneys, and official information sites repeated this message to the general community [28]. However, the latest data on the pharmacokinetics of aluminum has proven that this claim is incorrect [25, 29-33].

As explained in previous sections, aluminum from foods and aluminum from vaccines have different chemical properties, and their absorption, distribution in the body, and elimination are, hence, different. Aluminum adjuvants have long been thought to promote a powerful immune response by forming extracellular "depots" that gradually release the antigen under the solubilization action of the fluid that fills the spaces between the cells [34,35]. This "depot effect" approach assumed that the aluminum adjuvants are entirely dissolved into Al^{+3} ions, which are then promptly excreted through urine. Bio-disposition experiments utilizing monitored isotopic ^{26}Al demonstrated that soluble injectable infusions (i.e., not particulate) aluminum citrate in human participants result in the clearance of 83 percent of the administered concentration in the urine and 1.8 percent in the excrement by day 13 after injection [36].

The residual 15% remained in the body for a quite long period (4 percent stayed unexcreted 1,178 days after injection), which could be due to the majority of residual aluminum being stored in bone, as seen in rats [37]. The "depot hypothesis" was debunked when researchers discovered that aluminum adjuvant particulates are only found in macrophages in human muscle [31], as well as mice, rats, and monkeys receiving injections with aluminum hydroxide [31,38].

This is significant because the hypothesized interstitial fluid disintegrating actions would be ineffective in the situation of fast cellular uptake of aluminum particles [39]. The "depot hypothesis" was rejected a few years ago, as proof has been obtained that immune-enhancement necessitates dendritic cell processing of the aluminum adjuvant, rather than adjuvant preservation of the antigen [40] or adjuvanted vaccine continuousness for more than 2 hours [41] at the injection location. In stark comparison to the rapid removal of soluble aluminum infused into the vein [36], the source investigation on particulate aluminum adjuvant bio-disposition conducted using the ^{26}Al isotope revealed that after injection into the muscle of the aluminum hydroxide in two rabbits; on the 28th day, less than 6% of ^{26}Al was excreted in urine [34]. This elevated concentration of aluminum hydroxide did not appear to cause concern, because the researchers' fundamental assumption at the moment was that the compound was constantly solubilized, and they did not expect cellular incorporation of aluminum hydroxide and its impact on the compound's destination [32].

Regarding the aluminum-based adjuvants' low solubility, the latest experiments have shown that aluminum particles are able to travel inside phagocytes towards regional lymph nodes, and subsequently to remote organs, like the brain, and they can be traced even one year after inoculation [29, 30, 42]. In subsequent studies, the unmistakable detection of aluminum adjuvant inside monocytes (Figs. 1 and 2) was confirmed [33,43]. The Trojan horse-like process whereby aluminum carried by macrophages penetrates the brain and produces gradual buildup due to an absence of recycling, thus being presumably culpable for the brain damage linked with the utilization of vaccines adjuvanted with aluminum [44]. Moreover, antigen-presenting cells (APCs) readily absorb

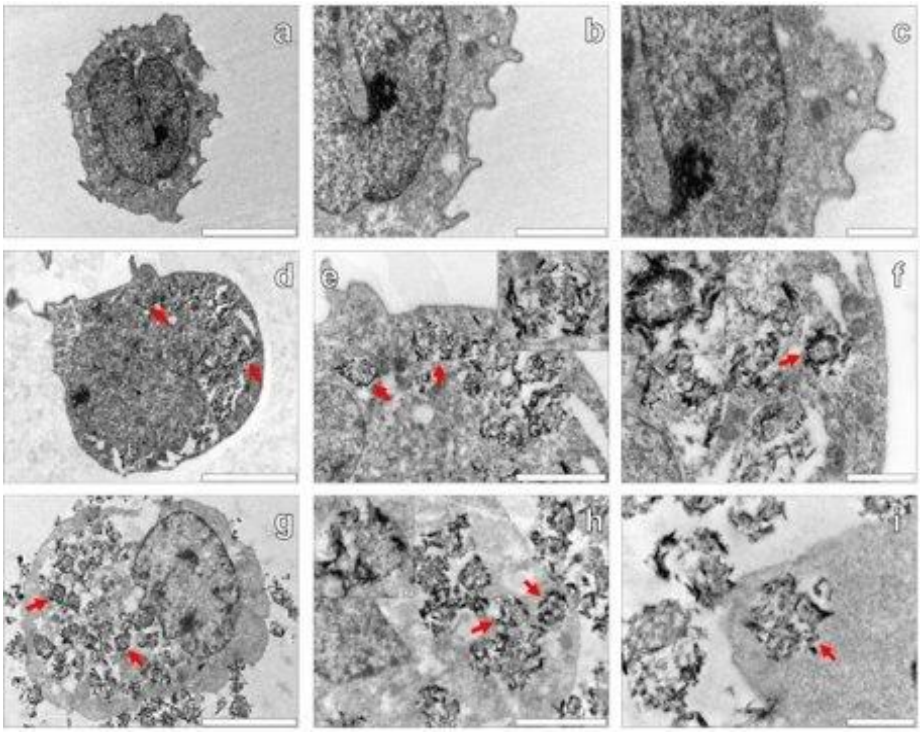

Fig.1. "Transmission electron microscopy (TEM) research of natural THP-1 cells (a–c), THP-1 cells co-cultured with 50 µg/mL AlO(OH) Sigma adjuvant (24 h) (d–f), and THP-1 cells co-cultured with 200 µg/mL AlO(OH)Sigma adjuvant (24 h) (g–i)".The Creative Commons CC-BY license governs the usage of this image, which allows for free use, sharing, and copying in every format as long as the original project is properly cited. Source: [43].

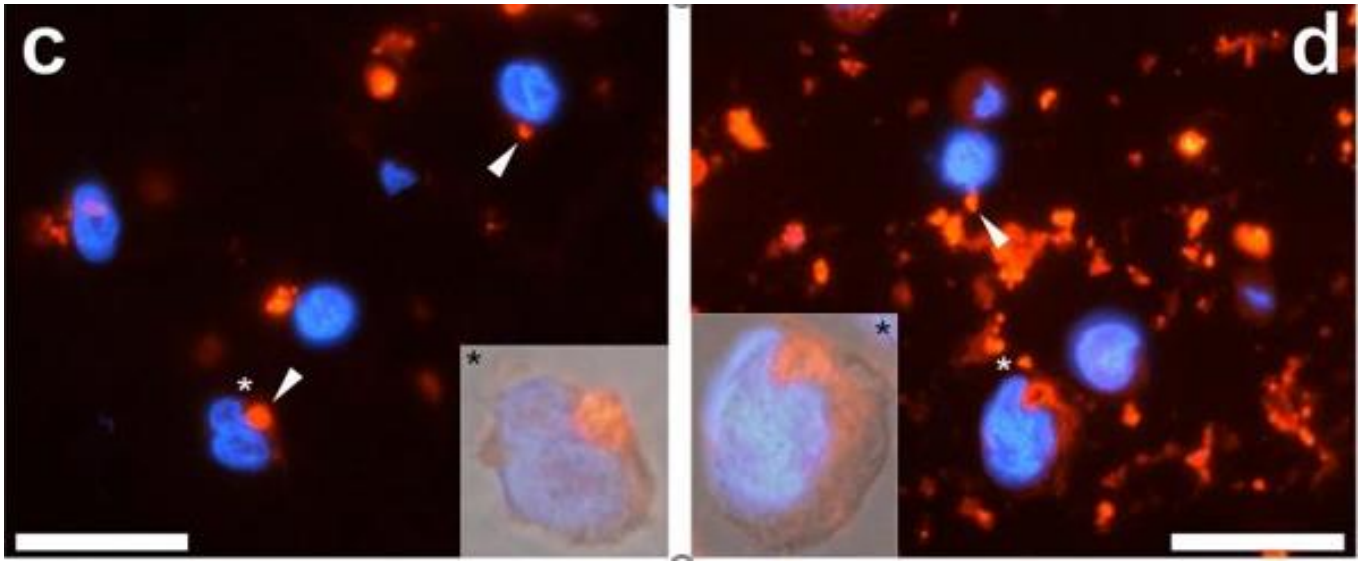

Fig.2.THP-1 cells (monocytes) co-cultivated with aluminum, colored with Lumogallion in agar-paraffin fixed (2 m slices). Augmented views of single cells are displayed in magnified inserts. Individual and identifiable adjuvant nanoparticles are highlighted with white arrows. Magnification × 1,000, scale bars: 20µm.
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alum nanoparticles [45], resulting in cells that live longer than normal [46] which obstructs alum removal [31,38,47]. Consequently, the very slow solubilization rate of Al adjuvant particles, especially Al hydroxide [25], makes the quantification of Al blood levels nearly useless to assess Al adjuvant toxicity (92).

Aluminum particles can be carried by monocytes to the lymphatic nodes, bloodstream, and the spleen, and equivalently to HIV, can employ a monocyte chemoattractant protein-1 (MCP-1)-dependent method to reach the brain [29]. This happens at a much-reduced level in ordinary circumstances, which explains aluminum's broad

tolerability notwithstanding its high toxic potential for neurons. However, constantly growing amounts of this sloppily degradable adjuvant in the community, on the other hand, could become insidiously dangerous, particularly in cases of over-immunization, a non-developed/modified blood brain barrier, or high inherent MCP-1 production [29].

Aluminum and Autism Spectrum Disorders (ASD)

Aluminum has a variety of negative consequences that impact the immunological and nervous systems, as in both adults and infants, it produces neurological and immunological toxicity [47], including deficiencies in neuronal transmission and the functional state of synapses, disturbance of the blood-brain barrier, microglial activation and inflammatory processes in the nervous system, genetic transcription deficiencies in the brain, dendrite injury, accumulation of amyloid fibrils, and alteration of genetic protection to autoimmunity. Several of the traits linked to aluminum neurotoxicity were also detected in persons with ASD [47].

Several groups have undertaken detailed analyses of the probable candidates for a possible genetic cause, however, rarely has a specific gene been identified as being responsible for the genesis of ASD [48,49,50]. Additionally, genes by themselves do not mutate at a fast enough rate to cause the current ASD epidemic [51]. The initial investigations of autism occurrence, done in the USA and Europe in the 1960s and 1970s, indicated a prevalence rate of 2 to 4 cases per 10,000 children, and as a result, the public perception of autism was that it was an uncommon infant syndrome [52,53,54].

Autism prevalence surveys in the United States, nevertheless, have shown a substantial rise in the disease's frequency in recent decades [53,55,56]. A counter-argument claims that the annual incidence of autism has remained constant over the last 20 years, the noticeable increases are attributed to (a) novel and diversified clinical definition, (b) clinicians who are better at recognizing the condition, (c) increased consciousness between family members and pediatricians, contributing to a predisposition to classify unconnected illnesses with ASD, (d) an enhance in the wider public, and (e) genetic predispositions [57].

However, the abrupt elevation in the occurrence of ASD could not be understood solely by heredity, or by modifications in diagnostic screening tools, which have evolved more rigorous in many aspects [58]. For example, 657 of the 933 participants investigated during the DSM-IV (Diagnostic and Statistical Manual of Mental Disorders, fourth edition) research study had a clinical diagnosis of ASD, while 276 had a non-autistic illness, according to a study. When applying the recommended DSM-5 inclusion criteria for ASD, just 60.6 percent of the cases having a clinical diagnosis of ASD satisfied updated DSM-5 diagnostic requisites for ASD [59]. As a result, the hypothesis that the rise in ASD incidence is related to a new and broader diagnostic criterion should be investigated in depth.

From a quantity of 10 in the late 1970s to 32 in 2010 (18 of which involve aluminum), the number of vaccines required for school entry has increased, according to an assessment of the essential data [60]. Notwithstanding extensive study initiatives focused on determining the likely contributing factors of the "autism epidemic," the academic literature has yet to provide a satisfying explanation [61]. Nevertheless, the evidence that ASD incidence has been significantly growing over the previous two decades clearly implies that some environmental variables might be implicated in the genesis of ASD [61]. Early life immunological impairments (before and after birth) caused by numerous toxic compounds are currently intimately related to the development of the autism spectrum disorder [62].

There is now minimal disagreement on aluminum's neurotoxicity. Nonetheless, the pharmaceutical sector and government entities nowadays believe that the relatively low concentrations of aluminum used in vaccines pose no health threat [17,63] and that the advantages of utilizing immunizations enclosing aluminum adjuvant far overcome any speculative dilemmas [64].

The FDA-approved aluminum concentration of 850 μg (0.85 mg) per vaccine was deduced from data showing that this quantity of aluminum per injection was able to improve the vaccine's antigenicity and potency [63,65], though did not take into account safety implications nor adapt the equations for a child's corporal weight. It has been stated that it is ethically incorrect that vaccine adjuvants are not utilized to execute experimental safety investigations before to use on humans [66].

Concerning aluminum dosage, it was found that lower concentrations are more toxic for neurons than higher concentrations due to the dimension of alum nanoparticles is equivalent to aluminum dosage [19], and macrophages are able to swallow the tiny alum granules and carry them to the brain, beginning a chronic neurodegenerative cascade [67]. A recent investigation found proof of neurotoxicity induced by aluminum in the prefrontal cortex and hippocampus of rats injected with low alum concentrations, implying that human beings are exposed to the detrimental effects of aluminum on cognitive processing by inducing oxidant stress, even if they are in contact with too low amounts and resulting in impaired long-term memory capacity [68].

Furthermore, it has been proposed that the security of aluminum adjuvants added to vaccines, like other environmental elements that could represent a neurotoxic danger and with which the children are in contact, must be scientifically re-analyzed without further retardation [69], especially when the Centers for Disease Control (CDC) have reported a still rising occurrence of ASD, of 1 child in 54 in the USA [70].

Experimental studies modeling autism have also provided evidence that aluminum adjuvants can negatively impact social interactions [44,71,72,73]. A study in mice found lowered social interactions, higher anxiety, and impairment in vision and spatial learning and memory in mice injected in conformity with the U. S. pediatric vaccination protocol [42].

Recognizing the involvement of cytokines in embryonic neural development, other researchers wanted to see if the US pediatric immunizations had any post-administration consequences on blood cytokine levels in a mouse model [74]. Only in the acute-phase cohort were IL-5 levels in serum considerably greater in the V1 and V3 cohorts in comparison with the reference group. Regardless of if the sexes were evaluated together or independently, the two immunized groups had considerable increases in IL-5 concentrations. Additional cytokines (GM-CSF, VEGF-A, TNF-α, MCP-1, IL-10, IL-6, and IL-13) were influenced as well, but to a lower degree and in a sex-dependent way. These data support the hypothesis that full pediatric immunizations given during the postnatal period can impact at least some transient central nervous system processes in mice [74].

In rats, dendrites from axons in the hippocampus CA1 region showed structural changes when were administered with maltol aluminum, the spine density of dendrites was reduced, and long-term potentiation (LTP) suppression was dose-dependent, resulting in decreased learning and memory effectiveness in rats [75,76].

A contemporary human study compared the cognitive abilities of persons that had been in close contact with aluminum and also persons not exposed to working in an aluminum mine, with the goal of determining how aluminum poisoning affects cognition [77]. On the Mini-Mental State test, individuals who had been in contact with aluminum had a mean cognitive value of 21.34 (6.71). When adjusting the age, gender, and educational background, the exposed group had a 6.77-fold greater risk of cognitive decline when compared with the control group [77]. Although these findings are inconclusive in terms of establishing a causal link between aluminum adjuvants and ASD in humans, the importance of comprehensive animal research to assess the security of these adjuvants has been emphasized [78].

Aluminum in Brain Tissue in Autism

Pediatric vaccines containing aluminum adjuvants are an alternative indicator of baby aluminum poisoning, and their widespread usage has been linked to an increase in the occurrence of autism [51, 79]. In several Western countries, children will have gotten a cumulative number of 23–32 immunizations when they reach 4–6 years old [80], many of them with aluminum adjuvants, as part of regular pediatric vaccine protocols [81, 82).

It was explored whether aluminum contained in vaccines could be responsible for the reported growth in ASD occurrence in occidental countries using Hill's criteria trying

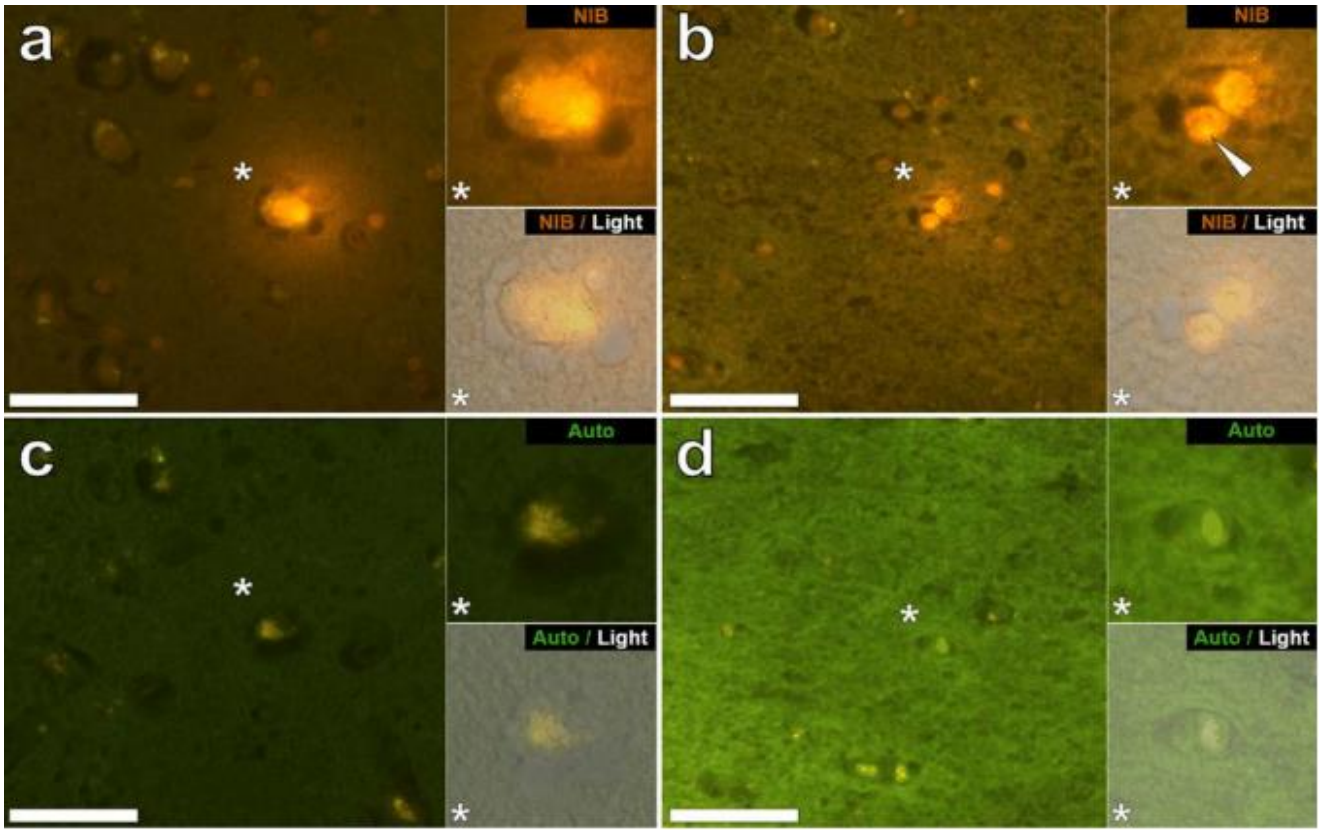

Fig. 3. "Lumogallion-reactive aluminium in likely neuronal and glial cells in the temporal lobe and hippocampus of a 14-year-old male donor (A10), diagnosed with autism. Intraneuronal aluminium in the temporal lobe (a) was identified via an orange fluorescence emission, co-deposited with lipofuscin as revealed by a yellow fluorescence in the non-stained autofluorescence serial (5µm) section (c). Intracellular punctate orange fluorescence (white arrow) was observed in glia in the hippocampus (b) producing a green autofluorescence emission on the non-stained section (d). Upper and lower panels depict magnified inserts marked by asterisks, of the fluorescence channel and bright field overlay. Magnification X 400, scale bars: 50µm". The Creative Commons CC-BY license governs the usage of this image, which allows for free use, sharing, and copying in every format as long as the original project is properly cited. Source: [83].

to identify if there is a causal relationship between aluminum contact and result. The findings revealed that:

1. Infants from the nations with the highest autism occurrence have the highest exposition to aluminum from immunizations [79].
2. Over the previous two decades, increasing contact with aluminum adjuvants was linked to a substantial rise in autism occurrence in the United States [79].
3. In seven Western countries, there is a substantial relationship between the quantity of aluminum injected to preschool kids and the present occurrence of this syndrome, specifically between the ages of 3 and 4 months. When the Bradford Hill criteria are applied to such information, it appears that the link between aluminum in vaccinations and ASD is causative [79].

In 2018, a pioneer study employed a special imaging technique to quantify the aluminum concentration in the brain (Fig. 3) of patients who died with an autism diagnosis [83]. When compared to the aluminum content of a normal brain (1.02 μg/g dry wt.) the aluminum concentration in the brain in autism was surprisingly elevated [84]. "For the occipital, frontal, temporal, and parietal lobes, the average aluminum concentration in 5 specimens were 3.82, 2.30, 2.79, and 3.82 μg/g dry weight, respectively" [83].

In these male ASD donors, the researchers also detected several of the greatest aluminum concentrations ever found in normal and diseased tissues, specifically 17.1 μg/g, 18.5 μg/g, and 22.1 μg/g dry weights; the age of the ASD donors distinguishes these results apart from prior studies of brain aluminum in other illnesses [83]. There are no equivalent reports in the scientific literature, with the nearest case involving a 42-year-old man with hereditary Alzheimer's disease who had equally high aluminum concentrations [85].

The discovery that aluminum was detected in all samples (10 of 10) of frozen or fixed brain tissue shows that people with ASD have extremely high concentrations of aluminum in their brains, perhaps implicating aluminum in the pathogenesis of ASD [83]. Another seminal work found that very low aluminum concentrations might be significantly harmful to the brain, resulting in glial activation and behavioral alterations in mice [19]. These findings show that there is no minimum safe aluminum concentration, as even low concentrations can accumulate over time and lead to the establishment of a neurotoxic pattern [26,39].

The Quest for Better and Safer Adjuvants

Although aluminum has been shown to be an effective adjuvant, proof of its neurotoxicity is growing. Antigens in vaccines, on the other hand, are unable to effectively trigger and enhance the immunological response without adjuvants [86]. Adjuvants are used to provide the 'danger' signal and activate the innate immunological system, resulting in vaccine stimulatory effects. The optimal candidate to substitute aluminum-based adjuvants is one that can create this "danger signal" while having no immediate or long-term collateral effects [87].

One of the potential candidates is the *Granulocyte Macrophage Colony Stimulating Factor* (GM-CSF), which is involved in the genesis, and enrollment of specialized antigen-presenting cells (APC). As a result, GM-CSF is an effective adjuvant [88, 89]. Furthermore, it causes a confined inflammatory reaction in the inoculation region, similar to what aluminum salts cause [90].

Calcium phosphate, which was employed for its good adjuvant properties in, tetanus, pertussis, diphtheria, and poliomyelitis vaccinations in France, is another contender. In the late 1980s, aluminum salts fully replaced it, but it is still used as a World Health Organization-approved adjuvant for human immunization [9]. While calcium phosphate has qualities similar to alum, it has the advantage of being an organic component of the human body and hence may be better tolerated. Calcium phosphate granules are biodegradable particles that are ingested by macrophages or dendritic cells through endocytosis and destroyed in the lysosome [91].

CONCLUSION

The paradigm shift proposing to reconsider the use of the alum-based adjuvants has to be carefully dissected to avoid incorrect interpretations. This proposal does not constitute an attack on vaccination, as nobody refutes the fact that it has been systematically proven to be effective in saving millions of lives. Unfortunately, scientists, who have empirically investigated the toxicity of aluminum-based adjuvants have been unfairly labeled as "anti-vaxxers". In fact, what they have been asking for is that the safety of aluminum as an adjuvant has to be re-evaluated by researchers and practitioners. A scientific paradigm must not become dogma. In fact, paradigms should be constantly updated, since what is considered an absolute truth today could change in the near future. The present work encourages researchers, health regulatory agencies, and pharmaceutical companies to allow themselves to think about the possibility that aluminum-based adjuvants could be toxic for susceptible children.

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Author Contributions

Conceptualization, A.R.C., V.N.U; E.M.R; Literature Review and Original Draft Preparation, A.R.C, V.N.U; E.M.R; Review and Manuscript Revision, A.R.C., V.N.U; E.M.R; Supervision, V.N.U; E.M.R; A.R.C. All authors have read and agreed to the published version of the manuscript.

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