Journal of Trace Elements in Medicine and Biology 51 (2019) 28–30

Contents lists available at ScienceDirect

Journal of Trace Elements in Medicine and Biology

journal homepage: www.elsevier.com/locate/jtemb

Letter to the editor

Testing new hypotheses of neurological and immunological outcomes with aluminum-containing vaccines is warranted

The evidence gathered following three lines of possible evidence for association of Aluminum (Al) use and Autism Spectrum Disorders (ASD), namely ecological comparisons, animal experiments and Al monitoring in brain), do not definitively prove any cause-effect relationship. However, there is even less evidence supporting the opposite conclusion that Al adjuvants are completely safe to use without any long-term downfall. Testing new hypotheses of neurological and immunological outcomes with Al-containing vaccines now appears as completely justified.

In recent years, several papers linking Autism Spectrum Disorders (ASD) and Aluminum (Al) adjuvants in vaccines have been withdrawn by the editors. In 2010, the "Lancet" formally retracted a 1998 paper [1] linking vaccine and autism. The paper suggested that there could have been a connection between autism and a triple vaccine for measles, mumps and rubella (MMR). Recently, the "Journal of Inorganic Biochemistry" retracted a 2017 paper [2] reporting of an animal study in mice linking Al-adjuvants and behavioral disorders. These retractions do not prove the allegation is false, rather, than the progress of science suffers of many biases.

Science progresses through the formulation and testing of hypotheses. Any aspect could be explained in different ways. Science must collect all the plausible explanations and filter them through testing. Hypotheses are supported when the actual observations match the expected observations. There are many works that are supportive of the safe use of Al-adjuvants in vaccines, and there are a few works that claim a link in between Al-adjuvants and autism. While the works that claim a link may certainly be partially or totally flawed, there is certainly no work that proves without any doubt that injection of Al as a vaccine adjuvant in early childhood is not harmful over a long-time window.

In between the works claiming a link between ASD and Al-adjuvants, there are three lines of scientific evidence suggesting correlation: ecological comparisons correlating immunization with Al-adjuvants and ASD, experiments in mice linking Al-adjuvants and behavioral disorders, and finally measurements of high concentration of Al in brain cells of subjects with ASD.

Al is neurotoxic, but it is used in many pediatric vaccines as an adjuvant [3–5]. There is therefore considerable speculation on the role of Al-adjuvants in vaccines in the rising ASD. Al is a neurotoxin and immune stimulator. Hence, it has in principle the potential to induce neuroimmune disorders. Dysfunctional immunity and impaired brain function are fundamental shortfalls in ASD.

Tomljenovic & Shaw [6] suggested a correlation between the rising ASD and the increased Al through vaccine adjuvants given during early postnatal life. The authors investigated whether exposure to Al from vaccines could contribute to the rise in ASD in the Western world. Their results showed that children from countries with the highest ASD frequency have the highest exposure to Al from vaccines. The increase in exposure to Al adjuvants notably correlated with the increase in ASD prevalence in the United States that was observed over the two decades prior of the study. A significant correlation was also shown between the amounts of Al administered to preschool children, mainly at 3–4 months of age, and the current prevalence of ASD in seven Western countries.

Tomljenovic & Shaw [7] argued that Al in adjuvants carries a risk for autoimmunity, long-term brain inflammation and associated neurological complications. Al may thus have profound and widespread adverse health consequences. In their opinion, the possibility that vaccine benefits may have been overrated, and the risk of the potential adverse effects being underestimated, has not been rigorously evaluated in the medical and scientific community.

Seneff et al. [8] investigated word frequency patterns in the United States Centers for Disease Control and Prevention (CDC) Vaccine Adverse Events Reporting System (VAERS) database. Their results provide evidence linking ASD and Al adjuvants in vaccines. Mentions of ASD in VAERS increased steadily at the end of the last century, during a period when mercury was phased out, while the load of Al-adjuvant was increased. Signs and symptoms significantly more prevalent in vaccine reports after the year 2000 include cellulitis, seizure, depression, fatigue, pain and death, which are also significantly associated with Al-containing vaccines. They argue that children with the ASD diagnosis may be vulnerable to toxic metals such as Al and mercury due to insufficient serum sulfate and glutathione. A correlation was also shown between ASD and the MMR (Measles, Mumps, Rubella) vaccine, partially justified via the increased sensitivity to acetaminophen administered to control fever.

Shaw et al. [9] noted anomalies in the behavior of mice injected with Al as per pediatric vaccination schedule. The animal model was developed to explore potential behavioral phenotypes and central nervous system alterations using injections of Al-hydroxide in early post-natal CD-1 mice, both male and female. Injections of a "*high*" and "*low*" Al adjuvant levels were calculated to correlate to either the United States or Scandinavian pediatric vaccine schedules. Both male and female mice in the "*high*" Al group showed significant weight gains following treatment up to sacrifice at 6 months of age. The male mice in the "*high*" Al group displayed important changes in light–dark box tests. They also showed alterations in various measures of behavior in an open field. The female mice showed significant changes in the light–dark box at both doses, though no significant changes of behavior in an open field.

Sheth et al. [10] further investigated the effect of Al adjuvants on the social behavior of mice. The study demonstrated a range of behavioral abnormalities in young mice after postnatal exposure to Al. Mice exposed to Al in early life unveiled a diminished social interest when compared to normal mice of same age.

Mold et al. [11] recently used transversely heated graphite furnace

https://doi.org/10.1016/j.jtemb.2018.09.006
Received 8 August 2018
0946-672X/

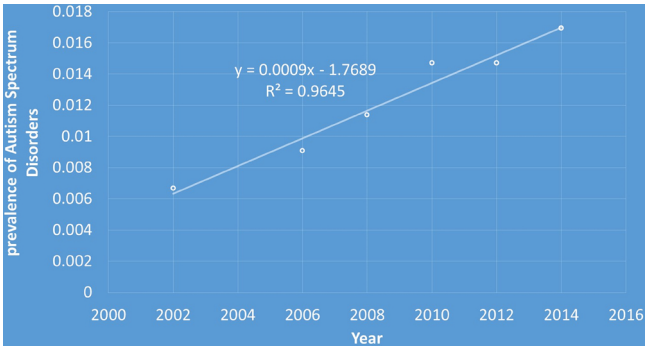

Fig. 1. Prevalence of Autism Spectrum Disorders in the last 6 United States CDC reports.

atomic absorption spectrometry to measure the Al content of brain tissues from donors with a diagnosis of ASD. They also used an Al-selective Fluor to identify Al in brain tissue using fluorescence microscopy. The Al content of brain tissue in ASD was steadily high. While Al was imaged associated with neurons, it appeared to be present intracellularly in microglia-like cells and other inflammatory non-neuronal cells in the meninges, vasculature, grey and white matter. Intracellular Al associated with non-neuronal cells was a fundamental observation in ASD brain tissue.

Lyons-Weiler & Ricketson [12] reported that Al levels in vaccine are based on immune efficacy but ignore body weight for safety. Safety inferences of vaccine doses of Al solely depend on dietary exposure studies of adult mice and rats. Infants may receive up to 17 times more aluminum than would be allowed with doses adjusted per body weight.

Lyons-Weiler & Ricketson [12] also found that the never retracted study by Mitkus et al. [13], which superficially found that the doses of Al in pediatric vaccines were safe, was seriously flawed as the presumption of toxicity was derived from a single study [14–16], that used ingested, not injected, forms of Al in adult, not infant mice.

A growing number of biomedical physicians and researchers have carefully reviewed the evidence for concern over Al and ASD [17,18].

Also, to mention, despite synergistic toxicity of Al and mercury is known, studies of adverse neurological and immunologic outcomes in children receiving both thimerosal-containing influenza vaccines and Al in the same visit, or the same month, have not been conducted [19].

All these works support the view that Al adjuvants, if applied by injections in the early period of postnatal development, may then affect the social behavior of humans, albeit no definitive conclusion can be taken based on these studies.

The United States CDC admits the prevalence of ASD increased of 15%, to one in 59 among children aged 8 years in 2014, from the prior report two years earlier, the highest prevalence since the CDC began tracking ASD in 2000 [20]. The prevalence of ASD among the CDC 11 surveillance sites is increasing, Fig. 1.

In the 2007 report, that looked at 2000 and 2002 data, ASD was detected one in 150 children. In the 2009 report, that looked at 2006 data, ASD was detected one in 110 children. In the 2012 report, that looked at 2008 data, ASD was detected one in 88 children. In the 2014 report, that looked at 2010 data, ASD was detected one in 68 children. While in the 2016 report, that looked at 2012 data, ASD was detected one in 68 children same of the reports of two years before, in the 2018 report, that looked at 2014 data, ASD is further increasing at one in 59 children. Consistent with previous reports, boys were four times more likely to be identified with ASD than girls. The rate is one in 38 among boys, and one in 152 among girls. There is an increasing incidence of ASD at a rate of $+0.9{\cdot}10^{-3}$ cases per year, that, if we do not consider Al adjuvants, still lack of any cause.

The three above lines of possible up to now available evidence for association of Al-use and ASD, ecological comparisons correlating immunization with Al adjuvants and ASD, Al-exposure and behavioral changes in mice, Al monitoring in ASD brain, do not fully prove a cause-effect relationship. Mold et al. [11] are another hint for Al related to ASD, but still the causative link on a molecular basis is missing. There is certainly a need of further animal experiments, and even more than that, investigation of molecular pathways likely explaining how Al could act in a way that ASD is increasing.

While there may certainly be not enough "*hard data*" evidence to claim that Al-adjuvants in vaccines are responsible for ASD, there is even less evidence supporting the opposite conclusion that Al- adjuvants are completely safe to use without any long-term downfall.

Testing new hypotheses of neurological and immunological outcomes with Al-containing vaccines is now seen as warranted, and not any more "*shifting hypotheses*" as previously written [21].

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