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Review

Empirical Data Confirm Autism Symptoms Related to Aluminum and Acetaminophen Exposure

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Abstract: Autism is a condition characterized by impaired cognitive and social skills, associated with compromised immune function. The incidence is alarmingly on the rise, and environmental factors are increasingly suspected to play a role. This paper investigates word frequency patterns in the U.S. CDC Vaccine Adverse Events Reporting System (VAERS) database. Our results provide strong evidence supporting a link between autism and the aluminum in vaccines. A literature review showing toxicity of aluminum in human physiology offers further support. Mentions of autism in VAERS increased steadily at the end of the last century, during a period when mercury was being phased out, while aluminum adjuvant burden was being increased. Using standard log-likelihood ratio techniques, we identify several signs and symptoms that are significantly more prevalent in vaccine reports after 2000, including cellulitis, seizure, depression, fatigue, pain and death, which are also significantly associated with aluminum-containing vaccines. We propose that children with the autism diagnosis are especially vulnerable to toxic metals such as aluminum and mercury due to insufficient serum sulfate and glutathione. A strong correlation between autism and the MMR (Measles, Mumps, Rubella) vaccine is also observed, which may be partially explained via an increased sensitivity to acetaminophen administered to control fever.

Keywords: autism; vaccines; MMR; HEP-B; glutathione; sulfate; cholesterol sulfate; aluminum; mercury; acetaminophen

PACS Codes: 87.19.xm; 87.19.xt; 87.19.xw; 87.18.Vf; 87.18.Sn; 87.19.lk; 87.19.lv; 87.19.um; 87.19.uj

1. Introduction

Autism, and, more broadly, autism spectrum disorder (ASD), is a condition characterized by impaired cognitive and social skills [1], along with a compromised immune function [2–5]. It can now no longer be denied that the incidence of ASD is alarmingly on the rise in the U.S. [6]. While it has been suggested that the observed increase in rates may be due mainly to a change in diagnosis criteria, the actual criteria have changed very little from 1943 to DSM-IV-TR [7–9]. Despite considerable research efforts devoted to trying to uncover the cause(s) of autism, thus far no definitive answer seems available from the research literature. However, the fact that ASD rates have been rapidly increasing over the last two decades strongly points to an environmental component. Indeed, autism is recently being reframed from being a strictly genetic disease to representing a complex interaction between genetics and environmental factors, suggesting that we should focus our attention more on "environmentally responsive genes" [10].

The ASD community has maintained a long-standing conviction that vaccination plays a causative role in ASD [11], an idea that has been vehemently denied by the vaccine industry [12], but nonetheless is still hotly debated [13]. A study published in 2011 has confirmed a positive correlation between the proportion of children who received vaccinations in each state over the interval from 2001 to 2007 and the incidence of autism or speech and language impairment [14]. For each 1% increase in vaccination rate, 680 additional children were diagnosed with autism or speech delay.

In [15], we proposed that a causative factor in autism is an inadequate supply of cholesterol sulfate, both *in utero* and postnatally. Cholesterol sulfate synthesis in the skin is catalyzed by sun exposure [16]. We hypothesized that autism may be induced by a combination of inadequate dietary sulfur and insufficient sun exposure to the skin, for both the mother and the child. A meta-study involving oxidative-stress related biomarkers present in association with autism identified a consistent deficiency in reduced glutathione [17], an important sulfur-based antioxidant that also plays a role in detoxifying aluminum. We proposed that cysteine, the rate-limiting amino acid involved in the synthesis of glutathione [18], is depleted through redirection into an alternative pathway to produce sulfate, due to the impaired sulfate synthesis from thiosulfate in the skin.

A recent study of biomarkers for 28 individuals with an ASD diagnosis showed reduced glutathione, cysteine, and sulfate compared to controls, and the authors proposed that a reduced detoxification capacity might impede mercury excretion [19]. These same authors observed a marked reduction in serum sulfate in association with ASD in another paper [20]. In particular, the level of free sulfate in the blood stream was only 33% of the level found in control subjects. We hypothesize that sulfate deficiency results in insufficient ionic buffering in the vasculature, with grossly inadequate sulfation of the extracellular matrix proteins that are essential for proper colloidal suspension of particles and cells [21,22].

Glutathione [23] and sulfate [24] are also essential for the detoxification of xenobiotics and commonly administered drugs like acetaminophen in the liver. Selenium, a trace metal in the same column of the periodic table as oxygen and sulfur, has been shown to protect against acetaminophen toxicity [25], and it has also been shown to be severely depleted in hair and nail samples from individuals on the autism spectrum [26].

A possible link has been found between acetaminophen and both autism and asthma [27]. The association of both asthma [28] and eczema [29] with ASD can be explained as an inadequate supply of filaggrin, due to the fact that cholesterol sulfate in the epidermis stimulates the production of profilaggrin, its precursor [30]. Filaggrin plays an essential role in maintaining the epithelial barrier [31], and its impairment leads to increased risk of both asthma [32] and eczema [33,34]. Thus cholesterol sulfate deficiency provides an explanation for the multiple links among autism, acetaminophen, asthma, and eczema.

It has been demonstrated that chronic aluminum exposure in rats induces depletion of glutathione in the liver as well as a significant reduction in the synthesis of bile acids [35], which are conjugated with taurine, the only sulfonic amino acid [36]. Taurine administration in conjunction with aluminum greatly ameliorates the adverse effects of aluminum on the liver, and this was explained as possibly due to the ability of the sulfonate group in taurine to bind with heavy metals such as aluminum [37]. These results suggest that glutathione and taurine are both involved in aluminum detoxification in the liver.

Many children with autism have a low amount of serum glutathione, with a larger fraction of it oxidized to GSSG [38]. Furthermore, increased use of antibiotics leads to an alteration in gut flora which impairs the ability to detoxify toxic metals like mercury. Dimercaptosuccinic acid (DMSA), an organosulfur compound with two thiol groups, has been found to be effective in ameliorating the symptoms of autism in placebo controlled studies [39], likely through its ability to enable the excretion of toxic metals such as lead and mercury [40]. It also led to a normalization of glutathione levels in red blood cells [40].

Vitamin D deficiency has been hypothesized to be a risk factor for autism [41]. The over-zealous application of sunscreen is strongly implicated in autism, not only because sunscreen interferes with the production of vitamin D_3 and cholesterol sulfate but also because it often contains aluminum, particularly the high Sun Protection Factor (SPF) sunblock products. Aluminum, due in part to its +3 ionic charge, is highly toxic to biological systems [42,43] as will be described more fully in Section 2.1. Indeed, there are no known life forms that utilize aluminum in any biological systems. The poorly developed barrier function of the autistic child's epidermis would likely lead to an increased penetration of aluminum through the skin. Furthermore, their serum sulfate deficiency leads to an impaired ability to dispose of aluminum. Aluminum would therefore be expected to accumulate over time, and, due to increased permeability of the blood brain barrier associated with autism [44], would almost certainly interfere with neuron function.

In the next section, we examine the evidence from the literature that aluminum toxicity may play a role in vaccine adverse reactions, and we describe available theories for the mode of toxicity of aluminum and other toxic metals.

2. Aluminum and Mercury in Vaccines

It has recently been proposed that aluminum, commonly used in vaccines as an adjuvant, may be the most significant factor in adverse reactions, and, furthermore, that the nervous system is especially vulnerable to aluminum toxicity [45]. Vaccine clinical trials often include aluminum in the placebo, at the same or greater concentrations than the amount found in the vaccine [46–49]. A comparable number of adverse reactions between vaccine and placebo in these trials suggests that aluminum is an important source of toxicity in the vaccine. Indeed, intraperitoneal injection of aluminum-adsorbed vaccine in mice caused a transient rise in aluminum in brain tissues [50].

The Food and Drug Administration (FDA) has set an upper limit of 5 micrograms Al/kg/day for neonates and individuals with impaired kidney function [51]. A highly informative recent review of a possible relationship between aluminum toxicity and Alzheimer's disease [52] also discussed issues related to the aluminum burden in children's vaccines. There, it was pointed out that children today receive a cumulative aluminum burden from vaccines that may exceed the FDA limit by a factor of 50.

The vaccine industry has a difficult task in designing vaccines that are both safe and effective [53]. The use of weakened but live pathogens can lead to vaccine-induced disease in children with an impaired immune system, yet debris from *dead* pathogens may not always cause a sufficient reaction to induce the production of antigen-specific memory CD8 T-cells, required for protection against future exposure. The industry widely reports success in creating vaccines with dead pathogens by adding adjuvants such as aluminum, lipopolysaccharide (LPS) from *E. coli*, and polycationic surfactants, to further stimulate the immune response [54]. It remains unclear exactly how aluminum achieves its effect of enhancing the immune reaction, but aluminum adjuvants are now thought to impact on humoral systems via their positive influence on the inflammasome complexes [55].

Another industry-claimed basis for adding aluminum or mercury to vaccines is to increase the stability of the antigen in long-term storage. It has been shown that the rate of acid-catalyzed hydrolysis of glucose-1-phosphate is significantly slower when the molecule is adsorbed to aluminum hydroxide adjuvant, increasing the effective pH of the environment by 2 pH units [56]. This effect would however also interfere with the human body's ability to break down the antigen from the vaccine, which may partially explain the heightened immune reaction.

Based on concerns that the mercury (49.6% by weight) in thimerosal might be contributing to autism [57], the industry made an effort to significantly reduce the amount of mercury present in vaccines beginning in the late 1990's [58]. In parallel, they began storing the vaccines in individualized glass vials—to avoid the ostensible need for a preservative to reduce the danger of contaminating repeated invasions of multidose vials. However, this raises another concern, as aluminum can be leached out of the glass vial and the rubber stopper during storage [59]. This same issue can also affect premature infants given serum albumin infusions, resulting in an inadvertent exposure to aluminum very early in life [60].

Glass contains aluminum oxide at levels ranging from 1.9% to 5.8% [61]. Leaching from a container is an ongoing process until the product is used. Storage containers contribute significantly to aluminum contamination in human serum albumin products. Because of impaired renal function, dialysis patients are at risk to developing encephalopathy and a severe form of dementia due to their inability to dispose of the small amounts of aluminum that could be present in the dialysis water base [62],

although this problem has been largely corrected today. We suggest that the effect of aluminum on the brain of a person already on the autism spectrum may manifest a similar pathology.

Mechanisms of Aluminum and Mercury Toxicity

Aluminum is one of the most common elements on Earth, yet no biological system has yet found a use for it. Aluminum is expected to induce biosemiotic entropy through multiple pathways [22,63,64]. Its +3 charge and highly kosmotropic properties make it extremely destructive in water-based biological systems. One purely biophysical mechanism might involve its direct effect upon interfacial water tension. Another less direct mechanism might involve competition for calmodulin binding and the initiation of a signaling cascade with profound consequences. Both phenomena would likely induce biosemiotic entropy through both supramolecular and epigenetic effects. Thus, a focus limited solely to genetics and molecular biology is likely to be misguided. Long-range, dynamically-structured interfacial water is the medium which, when energy-loaded, both conveys the biological message and overcomes the thermal diffusion problem [65,66]. When interfacial water is energy-unloaded, the biological message is corrupted: unfolded protein responses and apoptosis follow. We posit that aluminum is a *sine qua non* of biosemiotic entropy—an exogenous interfacial water stressor.

Since aluminum is a known neurotoxin, there is no safe level. The central nervous system is particularly susceptible to the deleterious effects of aluminum. Exposure of human neuronal cells to a low concentration (100 nM) of aluminum sulfate induces a response that emulates the gene expression changes associated with Alzheimer's disease [67]. Recently, a group of researchers investigated the effect of aluminum sulfate on an *in vitro* culture of human neural cells [63], which was directly compared to the effect of magnesium-, iron- and zinc sulfate. They confirmed that, by contrast with the other salts, aluminum sulfate had an unusual and significant ability to induce NF-κB signaling and subsequent reactive oxygen species (ROS), mediated by down-regulation of the important inflammation inhibitor, complement factor H (CFH). In a subsequent paper, the sulfates of 13 different cations were assessed for their ability to induce ROS in neuronal cultures, and aluminum was determined to stand out among all the ions studied for its remarkable ability to induce ROS, even compared with mercury and lead [64]. Aluminum induced a response that was a factor of seven higher than that of mercury and a factor of three higher than that of lead.

Aluminum adjuvants damage and rupture the phagolysosomes, generate reactive oxygen species, and induce potassium efflux from the cell [68]. Our research has led us to suspect disruption of calmodulin (CaM) signaling as one of the most destructive aspects of aluminum toxicity. CaM functions as a calcium sensor and signal transducer that regulates a number of distinct protein targets, influencing many different cellular functions [69]. Upon binding to calcium, CaM undergoes a conformational change, and subsequent transformations such as phosphorylation, acetylation, and methylation can modulate its action.

The aluminum ion is a potent inhibitor of voltage-gated calcium channels in the brain [70]. Normally, calmodulin (CaM), after binding to calcium, stimulates nitric oxide (NO) production by both endothelial nitric oxide synthase (eNOS) and neuronal nitric oxide synthase (nNOS). An investigation of the interaction of aluminum ions with bovine brain CaM [71], confirmed that aluminum binds to CaM with an affinity that is an order of magnitude stronger than that of calcium.

numbers in their table, one can compute a 41% increased relative frequency of autism diagnosis in the vaccinated versus the unvaccinated population in this age range, a number that might well have been statistically significant had it been singled out.

Finally, it is likely that other vaccines in addition to MMR play a role in autism, particularly since, unlike many vaccines, MMR contains neither thimerosal nor aluminum. MMR is often administered simultaneously with DTaP, an aluminum-containing vaccine. The synergistic and cumulative effects of multiple vaccines would likely lead to nonlinear enhancement of adverse events.

It has been claimed that Denmark had excluded thimerosal from all vaccines prior to the birth of any of the children in the study [86]. If this is true, then this is in stark contrast to the U.S. policy, where thimerosal still appears in several vaccinations given to young children, including Hep-B and HiB Titer. Aluminum is present in several of the vaccines, for example, Hep-B, PREVNAR, all of the DTaP formulations, and H1N1 flu vaccine multidose vials.

3.2. Other Related Work

Aluminum adjuvants are the only adjuvants approved for use. They are known to enhance the specificity, intensity, and duration of the immune response, leading to improved long-term protection from the disease [87]. A workshop was held in 2002 in San Juan, Puerto Rico, addressing the issues associated with aluminum in vaccines, with a particular focus on myalgias and fatigue in adults following vaccination exposure to aluminum [88]. A recently published article seriously addresses the question of the safety of aluminum adjuvants in vaccines, pointing out the neurotoxicity of aluminum [45]. A U.S.-based study published in 2010 [89] determined that a three-fold increased risk to autism was associated with neonatal administration of Hepatitis B (Hep-B) vaccine prior to 1999, compared with either no vaccination or a delay until after the first month of age. Notably, Hep-B contains both aluminum and mercury.

Several researchers have reported increased frequencies of either sudden death or other health crises such as anaphylaxis or cardiorespiratory problems in association with vaccines. In [90], it was reported that six infants died suddenly within 48 hours of having received a hexavalent vaccine, a frequency that is abnormally high compared to the risk of SIDS in the general population. Unexpectedly high SIDS rates following vaccination are also reported in [91]. Researchers in Italy [92] report that the first vaccination carries an increased risk to SIDS in infants. In [93], through statistical analysis based on 300 cases of unexplained sudden death, a 16-fold increased risk was determined following the fourth dose in a series of vaccinations. In [94], it was reported that the observed rate of anaphylaxis following administration of the HPV vaccine to females aged 12 to 26 was significantly higher than the rate observed following other vaccines. In [95], precautionary monitoring is recommended following vaccination of premature infants, due to observed adverse reactions related to cardiorespiratory events, as well as a substantial increase in serum levels of C reactive protein, an inflammatory marker. This was particularly true for DTaP, an aluminum- containing vaccine, especially when it was combined with concomitant vaccines.

Goldman and Miller [96] have previously examined the VAERS database, specifically looking at hospitalization rates and mortality statistics as a function of the number of vaccines simultaneously administered and of age. Linear regression analysis revealed several statistically significant trends,

including a positive correlation between hospitalization rates and number of vaccine doses. In addition, mortality rates for infants under six months were significantly higher than rates for children between six months and one year of age, suggesting increased sensitivity of neonates. The authors suggested delaying administering of vaccines as a strategy for reducing risk of a severe adverse reaction. These authors also emphasize the value of VAERS as an important postmarketing safety surveillance tool.

Studies on adverse reactions for vaccination of adults have also been performed. A 2002 study of the VAERS database related to Hepatitis B vaccine confirmed a significant number of adverse reactions in adults [97]. A case study published in 2009 described an adult's profound adverse reaction to multiple vaccinations containing aluminum, resulting in aluminum hydroxide deposits accumulating in macrophages in muscle cells, along with debilitating muscle pain and weakness associated with chronic fatigue syndrome and macrophagic myofasciitis [98].

4. Our Studies with U.S. CDC VAERS Database

The Vaccine Adverse Event Reporting System (VAERS) is a surveillance system implemented by the U.S. government, which allows doctors and/or patients to report any adverse reactions observed in association with vaccines. The cover page emphasizes that the data report only an association rather than a confirmed causal relationship. Data are readily available for download from the web site, "http://vaers.hhs.gov/index" beginning in the year 1990. In this section, we will present the results of several experiments we conducted with the VAERS database, using standard statistical techniques based on word frequency information.

In order to validate our methods, we first examined the differences between a set of records associated with autism and a comparison set drawn randomly from the remaining records. The autism-related data set contained all cases where the word "autism" or the word "autistic" showed up somewhere in the report. This yielded a total of 1,734 entries. The comparison set was constructed by randomly sampling from the remaining entries (~340,000 reports), but in such a way that the age distribution was exactly matched to the distribution obtained from the records associated with autism, obtaining a record of identical size (1,734) to that of the autism set. We performed a statistical analysis of selected words and phrases in the "symptom text" field as well as in the five "symptoms" fields in the associated VAERSSYMPTOM files.

We used an established method based on log likelihood ratio, as described in [99,100], which provides a *p*-value associated with the likelihood that the observed distribution bias of the word or phrase could have occurred by chance. To improve statistical power, we collected the most frequently occurring words in the "symptoms" fields, and organized them into reasonable classes. For example, "abdominal pain," "abdominal discomfort," "abdominal distention," and "abdominal tenderness" collectively represented the class "abdominal pain."

Table 1 shows all of the words or phrases that were biased towards the autism data set with a *p*-value at or below 0.05. Constipation [101], anxiety [102], asthma [28], eczema [29] and premature birth [103] have all been found to be associated with autism in the research literature. We consider it to be a validation of our methods that we detected these features with a statistically significant *p*-value. This also implies that the VAERS database may be useful for predicting associations between symptoms and conditions, irrespective of any claim about the effects of a particular vaccine.

Prematurity would be expected to be a risk factor for ASD, as the cholesterol sulfate supply from the placenta is normally greatly increased toward the end of pregnancy [104]. Premature infants may also suffer from additional aluminum exposure through albumin infusions [60].

Table 1. Skewed distributions of symptom words between two data sets: a set of vaccine adverse reactions associated with autism, and an age-matched set of other vaccine reactions. C1: number of entries in autism set containing this symptom; C2: Number of entries containing this symptom in the comparison set. *p*-value: the likelihood that the distribution would have occurred by chance according to a log-likelihood ratio formulation.

Symptom	C1	C2	*p*-value
Anxiety	49	2	0.011
Constipation	41	0	0.012
Infection	54	6	0.013
Ear infection	32	3	0.029
Eczema	18	0	0.044
Premature	20	1	0.046
Asthma	24	3	0.048
Pneumonia	19	1	0.050

Note: In this and subsequent tables, we use the word "symptom" inclusively to refer to signs, symptoms and conditions.

Three associated words suggestive of a weakened immune system, "infection," "ear infection," and "pneumonia" support the observation from the literature that autism is associated with immune dysfunction [2]. It has also been demonstrated that children with the autism diagnosis exhibit a heightened immune response to antigen stimulation [105], which we propose is caused by their global deficiency in sulfate supply. Thus, their increased vulnerability to infection in general likely parallels an increased likelihood of an adverse reaction to vaccines, particularly vaccines like MMR where the pathogen is only weakened but not killed.

4.1. Distribution of Vaccine Types in Autism versus Controls

Another aspect we investigated from the VAERS database is to compare the distribution of type of vaccine administered between the autism-related events and the non-autism-related events. The results are shown in Table 2. We looked only at data for children under 6 years old, and we computed the percentage of events associated with each vaccine type in each data set. As shown in Table 2, MMR was significantly more likely to be associated with autism (41% of the autism-associated events as against only 15% of the non-autism associated events, with a ratio of 2.67). HiB Titer and hepatitis were also over-represented in the autism group, although to a lesser degree.

Since MMR contains neither aluminum nor mercury, it is puzzling that children with the autism diagnosis seem to be highly sensitive to it. We have not examined the records in detail to determine what percentage had autism before receiving the vaccine, and, in fact, in many cases this information is not available from the VAERS record, which may simply list autism as a feature. An interesting theory relating the MMR vaccine to ASD involves a proposed toxic reaction to the acetaminophen (paracetamol) administered to control fever following vaccination [25,106]. It has been proposed that

acetaminophen may mediate oxidative stress and neurotoxicity in autism [107], and acetaminophen has been demonstrated to be toxic to developing mouse cortical neurons *in vitro* [108].

Table 2. Percentages of events associated with different vaccine types in the autism data set versus the not autism data set, and the ratio between the two. The numbers add up to more than 100% due to the fact that multiple vaccines are often simultaneously administered.

Pathogen	Percent Autism	Percent Not Autism	Ratio
MMR	40.94	15.35	2.67
Hep-B	16.02	8.71	1.84
HiB Titer	15.02	8.40	1.80
DTaP	42.53	43.93	0.97
Polio	15.60	16.34	0.96
Varicella	15.77	16.68	0.95
Pneumonia	8.81	10.29	0.86
Rotavirus	0.25	3.29	0.076
Total	**154.94**	**122.99**	**1.26**

A study of the ability of children with the autism diagnosis to dispose of paracetamol found that the ratio of paracetamol-sulfate to paracetamol-glucuronide (PS/PG) in the urine of children with severe autism following acetaminophen administration was significantly lower ($p < 0.00002$) than that measured for normal controls [109]. This result strongly suggests an impaired ability to metabolize toxic substances via a sulfation pathway. If the MMR vaccine is administered simultaneously with DTaP, an aluminum-containing vaccine (as is often the case), then the acetaminophen would likely interfere with the child's ability to dispose of the aluminum.

The autism-associated events exhibited an 84% increased frequency of reactions to hepatitis, and an 80% increased frequency of reactions to HiB Titer. While we included both Hep-A and B in the search, the matches were almost exclusively to Hep-B. Hep-B contains aluminum hydroxide and thimerosal, and HiB Titer contains thimerosal.

Hep-B is administered usually within 24 hours of birth, and most definitely in the first two months of life, and HiB Titer is administered three or four times before the age of 15 months. These two vaccinations would thus cause an accumulation of mercury and aluminum along with a depletion of the bioavailability of sulfate prior to the MMR vaccine in the vulnerable child, leaving them more susceptible to an infection arising from the live virus administered in MMR, and a subsequent dose of Tylenol (acetaminophen) to curb fever.

Another aspect we investigated was the number of events associated with autism as a function of the year the event was reported. Realizing that the report date and the event date can sometimes be separated by several years, we reported this detailed profile over time based on the event date instead of the report date. In cases where the event date was unavailable, we used the report date instead. The results are shown in Figure 1. It is striking that the number rises steadily over the last five years of the twentieth century, peaking around 2003. In the U.S., aluminum was allegedly phased in at the same time that mercury was phased out [110]. If the current CDC immunization schedule [111] is followed, babies are injected with nearly 5 mg of aluminum by 18 months of age.

result further supports the possibility that the aluminum in these vaccines administered to young children may be even more toxic than the mercury.

A highly significant correlation is found between "autism" and "Hep-B" ($p = 0.0014$), confirming the results reported in [89]. The association of aluminum-containing vaccines in general with autism does not quite make statistical significance ($p = 0.06$) compared to non-aluminum-containing vaccines. We explain this observation through the high fever associated with MMR, a non-aluminum-containing vaccine, that leads to the common practice of administering acetaminophen [25], which the autistic child cannot adequately detoxify. However, the fact that autism is so clearly associated with Hep-B gives one pause.

4.5. Limitations of the VAERS Database and the Experiments

Cases of vaccine injury are most likely vastly underreported by physicians to VAERS, as has been observed for physician reports of drug adverse reactions [115]. We identified only 1,734 mentions of autism in the entire dataset, whereas the National Vaccine Injury Compensation Program, established in 1988, reports over 5,000 claims that autism is associated with vaccines. Another limitation is that it is not easy to distinguish cases where autism may have been a preexisting condition affecting the child's sensitivity to the vaccine, as contrasted with cases where the vaccine may have preceded, and therefore may potentially be causative in, a later diagnosis of autism. Finally, both patients and physicians can submit reports, so quality control due to reporting bias or lack of expertise may be an issue. Not all of the reports contain a record of the date of the vaccination, and this introduces some error in the temporal relationships.

5. Discussion

Autism is a disorder affecting cognitive and social skills that has severe implications on the ability of the affected individual to lead a productive and independent life. The alarming increase in the incidence of ASD in the last decade suggests that, while genetic factors are contributory, environmental triggers must also play a decisive role. In this paper, we argue that ASD is a condition characterized by a serum deficiency in sulfur metabolites, particularly the sulfate anion, which results in an inability to safely dispose of mercury, aluminum, and acetaminophen.

While the autism community has focused on the mercury in thimerosal as the main culprit in vaccines, our studies with the VAERS database have identified aluminum and acetaminophen as being likely even more damaging than mercury. Aluminum binds strongly to sulfur-containing molecules, and the body depends on sulfur for the proper elimination of both aluminum and acetaminophen, as well as mercury. Because of the sulfur deficiencies, aluminum, mercury and acetaminophen likely accumulate in the autistic brain, leading to further damage.

In [116], it is argued that safety assessments for vaccines have not included appropriate toxicity studies because vaccines have not been viewed as inherently toxic, but that this point of view should be revisited in light of the increased awareness of the potential toxicity of aluminum, particularly for infants and young children. They argue further that it is now well established that a bidirectional neuro-immune cross-talk regulates both the immune system and brain function.

The incidence of autism-related adverse events in the VAERS database continued to rise over the time period after the amount of thimerosal in the vaccines had been sharply reduced. We hypothesize that this unanticipated consequence is due to simultaneous increases in the aluminum content, attributed to an increased number of required vaccines, intentional addition of aluminum to achieve an adjuvant effect, as well as the likely further accumulation of aluminum as a consequence of leaching, given the new practice of storage in individual glass vials with rubber stoppers. We identified several severe adverse reactions that were much more prevalent in reports from the second decade of the data, and showed that these same symptoms were also much more prevalent for reports involving aluminum-containing vaccines compared to reports on vaccines without aluminum, over the entire data set. These symptoms include seizure, cyanosis, gaze palsy, depression, fatigue, insomnia, and death.

Possibly contradictory to our proposal is a study which showed elevations of lead, mercury and uranium in hair analyses of 40 children with autism compared with 40 controls, but these authors found no elevation of aluminum in the hair [117]. However, the result on mercury contradicts another study which showed reduced mercury in the hair of infants with autism [118], and a third study which showed no statistical difference in mercury content of hair between children with autism and controls [11919]. A study in rats showed that oral antibiotics dramatically inhibit mercury excretion to 10% of normal levels [120]. It is conceivable that an inability to export aluminum into the hair, due to severe sulfate depletion, could complicate the interpretation of a metric based on aluminum content in hair.

The depleted supply of sulfate in the blood stream leads to increased vulnerability to vascular stress, in turn leading to excess immune cell activation, inflammation, permeability leaks, and blood clots, attributable mainly to a low ZP. This same deficiency interferes with the child's ability to dispose of the aluminum, which eventually accumulates in the brain and interferes with neural transmission. It is also likely that further aluminum exposure comes from aluminum in skin products such as high SPF sunscreen, particularly for the child whose barrier function is defective due to inadequate cholesterol sulfate and filaggrin in the epidermis. Other potential sources of aluminum are aluminum flocking agents in municipal water supplies, aluminum leaching from aluminum baby formula cans, and aluminum in the human milk supply to the breastfeeding infant, absorbed by the mother from sunscreen, antiperspirants, antacid medications, cooking utensils, *etc*.

Our specific studies on the MMR vaccine and the Hep-B vaccine further support our theories involving aluminum and acetaminophen toxicity. In an analysis of the distribution of vaccine types in events associated with autism versus the controls, we determined that MMR was highly over-represented in the cases associated with autism. A possible explanation is that the high fever associated with a reaction to MMR led to the administration of acetaminophen, whose safe disposal, like that of aluminum, depends on an adequate serum supply of bio-sulfates. The frequent presence of concurrent aluminum-containing vaccines would contribute synergistically to toxicity.

We hypothesize that the fever associated with MMR results in the administration of acetaminophen, which, in conjunction with the intense immune response to live viruses, becomes toxic to the vulnerable child. Most of the symptoms associated with Hep-B administration to children under 6 years old are also associated with aluminum-containing vaccines in general and over all age groups, further bolstering the hypothesis that the aluminum in the vaccine is a major source of toxicity. A strong association between Hep-B and autism also suggests that aluminum may contribute to autism.

This strong association does not however exclude mercury as a contributor to autism, given that Hep B has both mercury and aluminum. In fact, mercury and aluminum together may be synergistically toxic [113].

If our hypothesis is correct, then it should be relatively easy and very cost-effective to implement a solution to the problem. Both women of childbearing age and children should be encouraged to consume foods that are rich in sulfur and to spend considerable time outdoors without sunscreen on sunny days. It might be prudent to implement a screening test for sulfate and/or glutathione concentration in the blood prior to administration of an aluminum-containing vaccine, and to waive the vaccine or consider a non-aluminum-containing alternative if sulfate or glutathione levels are insufficient. A delay by one month of the current practice of Hep-B administration *at birth* seems warranted. The practice of including aluminum in the so-called "placebo" in vaccine trials should be abolished, so that the effects of aluminum adjuvant can be formally measured in a premarket phase. It would also be highly recommended to reconsider whether the increased immune response associated with aluminum adjuvant is worth the price in terms of increased risk of adverse reactions. Based upon our statistical research of the VAERS database, we would encourage the vaccine industry to consider omitting aluminum adjuvant doping of all vaccines for both children and adults.

In future work, we plan to create and maintain a web site where users can intelligently search the VAERS database, asking questions in spoken or typed natural language, such as, "Is there an association between miscarriage and the Gardasil vaccine?" An intuitive graphical interface will also help users easily find adverse event reports relevant to their personal experiences. This system will be modeled after a similar system we have already constructed for prescription drugs [121]. We believe that the VAERS database is a rich resource, many of whose secrets are yet to be revealed.

6. Conclusion

In this paper, we have presented some analyses of the VAERS database which strongly suggest that the aluminum in vaccines is toxic to vulnerable children. While we have not shown that aluminum is directly causative in autism, the compelling evidence available from the literature on the toxicity of aluminum, combined with the evidence we present for severe adverse reactions occurring much more frequently following administration of aluminum-containing vaccines as compared to non-aluminum-containing vaccines, suggests that neuronal damage due to aluminum penetration into the nervous system may be a significant factor in autism. The fact that mentions of autism rose steadily concomitant with significant increases in the aluminum burden in vaccines, is highly suggestive. However, it is possible that other factors, such as more aggressive reporting or simultaneous increases in other environmental toxins, e.g., herbicides or pesticides, or aluminum in other products such as antiperspirants and antacids, may have contributed to these observed increases. We also observed a strong correlation between the MMR vaccine and autism, which we suggest could be explained by the effects of acetaminophen.

We have proposed elsewhere that an impairment in cholesterol sulfate synthesis in the skin and in the vasculature may be causative in autism, and we argue here that vaccines can act synergistically with this impairment in the vulnerable child. We propose that simple corrective measures such as increased sunlight exposure and decreased use of sunscreen may help protect a child from a severe

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