Chapter 4
Aluminum as a CNS and Immune System Toxin Across the Life Span

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Abstract In the following, I will consider the impact of aluminum on two major systems, the central nervous system (CNS) and the immune system, across the life span. The article will discuss the presence of aluminum in the biosphere, its history, and the sources of the element. These include food, water cosmetics, some vaccines, and a range of other sources. I will also consider aluminum's unique chemistry. Finally, in humans and animals, I will consider how aluminum may impact the CNS at various levels of organization and how it may be involved in various neurological disease states across the life span. These disorders include those of infancy and childhood, such as autism spectrum disorder (ASD), as well as those in adulthood, such as in Alzheimer's disease. The bidirectional nature of CNS–immune system interactions will be considered and put into the context of neurological disorders that have an autoimmune component. I will argue that the exposure to humans and animals to this element needs to be reduced if we are to diminish some CNS and immune system disorders.

Keywords Aluminum bioavailability · Central nervous system · Immune system · Autoimmunity · Autism spectrum disorder

4.1 Introduction: Neurological Diseases and Causality Factors

An ongoing debate in any of the subfields of neurological disease research concerns the relative contributions of the putative factors to the origin and progression of any such disease. This debate occurs regardless of whether the disease in question is Alzheimer's disease (AD), Parkinson's disease (PD), and Lou Gehrig's disease (amyotrophic lateral sclerosis (ALS)) in older individuals or autism spectrum disorder (ASD) in children. In each case, the debated etiologies tend to include the

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following: genetic mutations/deletions or polymorphisms, environmental toxins, and some combination of both of these factors.

Included in environmental considerations are the emerging concepts about the role of a broad range of environmental impacts across the life span, i.e., the "exposome" [86]. This last may include potential toxic contributions from the microbiome of those so affected [23].

Until recently, most conceptualizations of neurological disease etiologies have focused rather narrowly on abnormal genetic factors. In relation to neurological diseases associated with aging, the concentration of effort in seeking genetic causes is arguably not warranted by the numbers of the so-called "familial" forms of AD, PD, or ALS compared to those forms considered to be "sporadic", or of unknown cause. The latter are usually considered to arise from environmental exposures to some toxin(s).

For these disorders, the percentages derived from autosomal mutations never exceed 10% of the total, regardless of how many new contributing mutations are found for those in the familial category [126]. One clear exception is Huntington's disease which has a clearly linked mutation.

As with the above diseases, developmental neurological disorders, for example, ASD and juvenile schizophrenia, do not show a uniformly dominant genetic etiology (as discussed in [122]). The studies to date on ASD, for example, do show some interesting genetic variations in those with the disorder, but these do not tend to be uniform across the ASD patient population. Some researchers have described each case as being like "snowflakes," meaning that each, while showing genetic deviations from the normal population, is nonetheless unique.

At the same time, studies of any of the sporadic neurological diseases cited above have failed to find a single environmental factor (see details and references in Shaw [122]), although such have been clearly indicated in several non-related neurological disease clusters, for example, those involving methyl mercury poisoning or lathyrism (see Shaw [122]).

An emerging view, albeit not necessarily a consensus one, is that most age-dependent neurological diseases at any stage of the life span likely arise due to some complex interplay of genetic susceptibility factors (and there can be more than one) and toxic exposures in any individual exposome (many more than one such factor) that may be relatively unique to any affected individual (for additional references, see Shaw [122]).

These considerations apply in particular to current views about ASD, an early onset neurological disorder characterized, in part, by abnormal social interactions and language development. This is partially because of evidence suggesting a rising incidence to those on this spectrum. It should be noted that not all of those in the field agree that incidence has changed, instead attributing the measured changes in rate to a combination of expanded diagnostic criteria and greater social and medical awareness of the condition. While these latter conjectures have become popular in some circles, rigorous evidence that either or both contribute to persistent incidence changes has not yet been produced. Indeed, some of those holding such views seem particularly concerned to move the discussion away from environmental factors,

and, in particular, from vaccines and the various components of vaccines, including aluminum (Al) adjuvants.

4.1.1 Aluminum Toxicity: General Considerations for the Impact on Human Neurological Diseases Across the Life Span

With the above as a general background, it will be worthwhile to consider aluminum in its various forms and routes of administration as a potential neurotoxin generally. More specifically, it is important to consider the role that aluminum exposure through various sources, including through routine pediatric vaccinations, may play in disorders of the developing central nervous system (CNS).

Finally, it will be important to discuss the intimate interrelationship, particularly in CNS development, with the immune system and how aluminum as a neurotoxin can impact both systems.

4.2 Aluminum in the Biosphere and Forms of Human Exposure

One element to which humans are currently heavily exposed is aluminum, whose ubiquity in the human biosphere has been steadily increasing for well over 100 years. Not only does aluminum toxicity has clear impacts on the CNS of animals and humans; it also negatively impacts other organ systems in both. It can also be toxic to plants (for reviews, see Tomljenovic [125] and Shaw et al. [139]).

The scientific literature is replete with examples of such toxicity, some of them going back almost to the earliest exposures to bioavailable aluminum derived from human activity. As noted by William Gies [52] over a century ago:

> These studies have convinced me that the use in food of aluminum or any other aluminum compound is a dangerous practice. That the aluminum ion is very toxic is well known. That aluminized food yields soluble aluminum compounds to gastric juice (and stomach contents) has been demonstrated. That such soluble aluminum is in part absorbed and carried to all parts of the body by the blood can no longer be doubted. That the organism can "tolerate" such treatment without suffering harmful consequences has not been shown. It is believed that the facts in this paper will give emphasis to my conviction that aluminum should be excluded from food. (p. 816)

Gies was also referring to even earlier studies, some from the early nineteenth century, starting with observations on the parenteral administration of aluminum salts [102] and with animal studies (Siem, as cited in Dollken [35]). Dollken [35], for example, showed instances of degeneration in the rabbit CNS following aluminum exposure.

Much of the literature on aluminum neurotoxicity will be discussed in Sect. 4.3 below, but it is important to note at the outset that it is still widely held, by some in both the medical and lay communities, and that aluminum is both inert and harmless. This view is then elaborated to propose that any potential for aluminum CNS toxicity to occur has been "debunked," to use a lay/journalistic term (see, e.g., Lidsky [84]), when in fact quite the opposite is the case.

Apart from careless scholarship, there are other reasons leading to the view that aluminum is not involved in neurological diseases. In part, some of the objections have arisen from what was perceived to be a lack of evidence for earlier claims that aluminum from various environmental sources posed a health risk, as suggested by McLachlan et al. [93]. Critics of McLachlan's work contended that human exposure to ionic aluminum exposure was, and remains, fairly minimal under most circumstances and thus could not play a significant role in neurological diseases. The McLachlan review may, however, have been prescient, in that while metallic aluminum is relatively inert, as are the various aluminum–silicate complexes, aluminum ions (Al^{3+}) can be released in acidic environments and are anything but benign.

4.2.1 Aluminum Chemistry and the Intersection of Aluminum with the Biosphere

Aluminum is the third most common element after oxygen and silicon on earth and the most abundant metal in the earth's crust. The abundance of aluminum on earth and the recent historical and current ubiquity in the biosphere have fostered attitudes such as that already mentioned, namely, that if it is so common, it cannot be harmful. However, as shown by Exley and colleagues [19–21] and others [139], this element was not widely bioavailable until recent historical times.

In regard to this last point, it may be notable that due in part to its historical lack of bioavailability, aluminum seems to have been "selected out" of involvement in terrestrial biochemical evolution [19, 43]. This situation changed with the industrial extraction of aluminum, primarily from bauxite, from the 1820s onward, and its myriad current materials applications have brought human beings into ever-increasing contact with various forms of the element.

Chemically, aluminum avidly binds to oxygen, carbon, phosphorous, and sulfur, all key elements in biochemical reactions in biological systems, and thus provides the potential to significantly impact such systems. In spite of claims often made in the context of aluminum's various industrial and medical applications, the element is therefore certainly not inert – nor, as will be shown below, is it harmless. It is also manifestly not an "essential" element, as erroneously previously claimed by some medical websites (e.g., the Children's Hospital of Philadelphia [22]).

4.2.2 Sources of Aluminum in the Biosphere

As already noted, aluminum has been linked to various disorders in plants, animals, and humans [42, 112, 120, 139–141], not least of which are those involving the CNS in animals and humans.

Aluminum in the biosphere, particularly that which may affect humans, arises from various sources [118]. It has a significant presence in processed foods, both through deliberate addition for its chemical properties and due to contamination during the manufacturing process. Salts of aluminum show up in a great variety of medicinal products, including antacids, various coatings for pills, and some vaccines. In regard to the latter, aluminum salts serve as adjuvants to improve the immunogenicity of antigens [141]. Aluminum salts are also used as mordants in cosmetics and in antiperspirants.

The release of ionic aluminum can occur in acidic conditions such as in acid soil or in various food preparations where acidic solutions are in contact with metallic aluminum. The former includes soils of volcanic origin and, increasingly, in soils exposed to acid rain. The latter has become an emerging feature of the human biosphere with the consequence that aluminum has become even more bioavailable than in previous decades (Exley, pers. comm.).

Food remains the most common source of human exposure to aluminum [158]. The second most common source appears to be from aluminum vaccine adjuvants [141]. In both cases, aluminum can readily enter the body by way of its soluble salts.

In the case of food, aluminum is absorbed through the gastrointestinal (GI) system with an average daily human range of 3–10 mg [158]. Intestinal absorption is influenced by compounds that increase absorption (e.g., citrate and fluoride) or is decreased by substances such as milk [137].

In addition, the acidity of some foods cooked in aluminum pans may serve to release ionic aluminum. Additionally, as most “tin” cans are actually made of aluminum and have been for a number of years, any acidic solution that breaches the protective epoxy coating, a bisphenol-A epoxy resin, will release potentially large amounts of ionic aluminum (not to mention bisphenol-A). This concern applies to cans containing fruit juices and various “soft” drinks. The structural integrity of the coating on aluminum cans can also be compromised by mechanical stress and/or heat [54].

Far beyond the possible release of aluminum ions from older cookware and current aluminum cans, aluminum finds its way into a variety of products for human use, as presented in the following subsection. In each case, the relative absence of obvious acute effects has led to a view similar to that which greeted the McLachlan study, namely, that human exposure to aluminum from most sources is unlikely to have a significant impact on human health. That this perception is largely incorrect is abundantly demonstrated every 2 years at the Keele University conference on aluminum (e.g., Keele University [75]).

Table 4.1 Sources of bioavailable aluminum in humans

Major sources of Al exposure in humans	Daily Al intake (mg/day)	Weekly Al intake (mg/day)	÷ PTWI[a] (1 mg/kg/bw; for an average 70 kg human PTWI = 70 mg)	Amount delivered daily into systemic circulation (at 0.25% absorption rate)
Natural food	1–10	7–70	0.1–1	2.5–25 μg
Food with Al additives	1–20 (individual intake can exceed 100)	7–140 (700)	0.1–2 (10)	2.5–50 μg (250 μg)
Water	0.08–0.224	0.56–1.56	0.008–0.02	0.2–0.56 μg
Pharmaceuticals (antacids, buffered analgesics, anti-ulceratives, antidiarrheal drugs)	126–5000	882–35,000	12.6–500	315–12,500 μg
Vaccines (HepB, Hib, Td, DTP)	0.51–4.56	NA	NA	510–4560 μg[b]
Cosmetics, skin care products and antiperspirants[c]	70	490	NA	8.4 μg (at 0.012% absorption rate)
Cooking utensils and food packaging	0–2	0–14	0–0.2	0–5 μg

[a]PTWI (provisional tolerable weekly intake) is based on orally ingested Al; generally only 0.1–0.4% of Al is absorbed from the GI tract; however, Al may form complexes with citrate, fluoride, carbohydrates, phosphates, and dietary acids (malic, oxalic, tartaric, succinic, aspartic, and glutamic), which may increase its GI absorption (0.5–5%). Co-exposure with acidic beverages (lemon juice, tomato juice, coffee) also increases Al absorption as well as conditions of Ca^{2+}, Mg^{2+}, Cu^{2+}, and Zn^{2+} deficiency

[b]A single dose of vaccine delivers the equivalent of 204–1284 mg orally ingested Al (0.51–4.56 mg), all of which is absorbed into systemic circulation. Al hydroxide, a common vaccine adjuvant, has been linked to a host of neurodegenerative diseases; it also induces hyperphosporylation of MAP tau in vivo

[c]The risk of antiperspirants is both from dermal exposure and inhalation of aerosols. Inhaled Al is absorbed from the nasal epithelia into olfactory nerves and distributed directly into the brain (From Shaw [122])

Table 4.1 highlights some of the key sources of bioavailable aluminum to which humans are exposed (excerpted from Tomljenovic [139]. See original article for relevant references).

Aluminum can appear in drinking water following the use of aluminum sulfate as a flocculant, but its overall impact seems to be low (0.3%) [158], except in unusual circumstances such as the large aluminum sulfate spill into the water supply in Camelford (United Kingdom) in 1988. High concentrations can also arise naturally in well water near volcanic or acidified soils.

The addition of fluoride to drinking water as part of a campaign against dental caries raises concern from two neurological perspectives, notwithstanding the

presumed – and, apparently, incorrect – value of water fluoridation for the prevention of tooth decay. First, fluoride promotes GI disorders [146]. Second, the joint presence of aluminum and fluoride can form aluminofluoride compounds which can act as phosphate analogues [137].

Aluminum can also enter the body by inhalation, with an estimated daily uptake of 4.4 μg in industrialized areas [101]. Aluminum metal workers may show higher levels in blood, urine, and bone [40, 53, 85]. Health outcomes of inhaled aluminum can include respiratory tract infections with asthma-like symptoms [78] and cognitive disorders [116], the latter implicating uptake into the CNS. A recently characterized apparent "cluster" of neurological diseases has been described in former miners who were deliberately exposed to aluminum powder by inhalation in an unsuccessful attempt to prevent silicosis [92].

Given patent kidney function, most dietary/waterborne aluminum ions will be excreted through the kidneys relatively rapidly. An additional major route of aluminum excretion is through sweat [95]. Notably, the same is not true for aluminum bound up in fluoride complexes or for aluminum that has a different route of administration, such as by injection into muscle or skin. Nor is it clear how much aluminum from inhalation is removed.

In regard to CNS levels, the amount of aluminum in the normal adult human brain is less than 2 μg/g [3], with the distribution reflecting higher concentrations in gray compared to white matter [18]. Along with bone, the brain has the highest potential to accumulate aluminum [42, 43]. Postmortem brain samples of individuals exposed during the Camelford incident showed an aluminum concentration of from 0.75 μg/g in frontal white matter to 49 μg/g in the choroid plexus [45]. The association of aluminum with the hallmark abnormal protein entities in Alzheimer's disease, amyloid beta (Aβ) plaques, and neurofibrillary tangles (NFTs) has been well documented [15].

There is disagreement about how much aluminum entering the brain is later removed [156] versus [76], although the differences in outcome may reflect the route of administration. However, retained aluminum seems to be stored in five main compartments: the blood–brain barrier, the brain interstitial fluid, neurons, glia, and, in pathological neurological diseases, in inclusions such as Lewy bodies, NFTs, and Aβ plaques [4, 79, 117].

4.2.3 Aluminum in Vaccines

As mentioned, one main source of aluminum, particularly in the very young, is its widespread use as a vaccine adjuvant, or "helper," acting to stimulate an immune response. There are a variety of aluminum adjuvant preparations, but the two most common are aluminum hydroxide and aluminum phosphate [16].

Although a single vaccine may contain only a relatively small amount (usually less than 0.5 mg of the adjuvant compound, not elemental aluminum), aluminum adjuvants may cumulatively constitute an important source of the overall aluminum

body burden. For example, the administration of 20 or more vaccines containing 0.5 mg aluminum compound as adjuvants would add up to an extra 10 mg aluminum compound to the body burden, equivalent to a normal dietary intake of aluminum of over 4000 mg/day [101].

Two considerations apply here. First, the circumstances in which aluminum from vaccines may be given in such amounts include the typical pediatric vaccine schedule of many Western countries and from various sources in war-time conditions. In the latter case, it is notable that Gulf War syndrome was associated, at least in part, with multiple vaccines given to potentially deploying soldiers. Many of these vaccines were aluminum-adjuvanted [66]. The second consideration is that aluminum adjuvants are not subject to the same pharmacokinetics as that of dietary/water aluminum exposure and do not seem to be efficiently excreted.

In regard to aluminum excretion, there are two key caveats to consider. The first is that the form in which aluminum is found is a major factor in its potential toxicity. Thus, not all aluminum adjuvants are likely to be identical in their potential impact. Nor have detailed studies compared the various forms [125]. Second, companies making such adjuvants usually employ proprietary forms of these compounds, which may have quite different properties to those that are more commercially available. The neurological pathologies associated with aluminum-adjuvanted vaccines administered to commercial sheep, to be described below, do not, however, support the notion that such proprietary forms necessarily have lesser neurological impacts than commercial forms of the same molecules [88].

4.3 Human and Animal Studies of Aluminum Neurotoxicity

In addition to the early evidence for aluminum's toxic actions on the CNS, more recent studies have clearly implicated this element in various human neurological disorders. A now-famous example termed "dialysis-associated encephalopathy" (DAE) occurred when kidney dialysis patients were accidentally given dialysis fluids containing high levels of aluminum [117]. The outcomes were typically of relatively rapid onset and severity. The resulting neurological signs included cognitive dysfunctions resembling Alzheimer's disease and epileptic seizures. Postmortem histology showed some of the hallmark pathological features of Alzheimer's disease, including NFTs and Aβ plaques. It is likely that the mechanism by which aluminum ions were transported into the brain involved one or more of the various carrier proteins, including ferritin and transferrin [119, 157].

Aluminum has been further linked to other neurological disorders across the life span, from Alzheimer's disease (see review by Tomljenovic [139]) in old age and to ASD in children [125, 140].

A variety of other CNS disorders of an autoimmune nature have also been associated with aluminum injections. These include macrophagic myofasciitis (MMF) [50, 51]which is a deteriorating neuromuscular disorder that follows intramuscular injections of adjuvant aluminum hydroxide. A sequela to MMF is often a form of

mild cognitive impairment (MCI) [115], sometimes viewed in other circumstances as a precursor to Alzheimer's disease. MMF also features a variety of disturbances in interhemispheric functions. Variations on the "autoimmune syndrome/inflammatory syndrome induced by adjuvants" (ASIA) disorders [69, 130], including MMF, may also occur.

Animal models of neurological disease using aluminum are available for ALS [109, 124], Alzheimer's disease [149–153], and, as cited in Tomljenovic [139], ASD [123, 126, 140]. In the first instance, subcutaneous injections of aluminum hydroxide in young male mice induce apoptotic neuronal death in motor neurons in the spinal cord and motor cortex, accompanied by degraded motor function.

Similarly negative CNS outcomes in more extensive experiments have been reported [29]. In addition, subcutaneous aluminum hydroxide injections in newborn mice induce significant weight increases in some cases and a range of behavioral changes associated with increased anxiety [123]. Aluminum-treated mice also show deficits in social interactions [127].

Adding yet another species, Lujan et al. [88] reported a neurological disorder in commercial sheep after a mass vaccination campaign against "blue tongue." The adjuvant in the vaccine was aluminum hydroxide. Chronic adverse effects were observed in 50–70% of flocks and up to 100% of animals within an affected flock. The behavioral disturbances and neurological signs included restlessness, compulsive wool biting, generalized weakness, muscle tremors, loss of response to external stimuli, ataxia, tetraplegia, and stupor.

As with human DAE, coma and death in the treated sheep could follow. On histological examination, inflammatory lesions in the brain and spinal cord were found associated with the presence of aluminum. These lesions included multifocal meningoencephalitis, demyelination, multifocal neuronal necrosis, and neuron loss in the spinal cord.

The disorder was made worse by cold weather conditions, perhaps suggesting some synergy with other environmental factors. These initial observations were successfully reproduced under experimental conditions following the experimental administration of aluminum-containing vaccines.

The veterinary studies by Lujan et al. [88] seem largely to confirm the general nature of the negative CNS outcomes previously seen in mice following aluminum adjuvant administration. In both mice and sheep, motor and cognitive function changes were noted. Degeneration of neurons in the CNS followed in both cases, particularly among motor neurons.

A key question is how aluminum might be transported from the site of injection into the CNS. The answer has been provided by the work of the Gherardi group which showed that aluminum hydroxide administered intramuscularly in mice does not stay localized in the muscle, but rather migrates to different organs. The path by which it does so is now clear from various tracking experiments with fluorescent markers, notably rhodamine- and nano-diamond-labeled aluminum hydroxide. These studies demonstrated that a significant proportion of the nanoparticles escape the injected muscle within immune cells (macrophages), travel to regional draining lymph nodes, and then exit the lymphatic system to reach the bloodstream, eventu-

ally gaining access to distant organs, including the brain. Such a "Trojan horse" transport mechanism, in which aluminum-containing macrophages enter the brain, predictably results in the gradual accumulation of aluminum due to lack of recirculation [29, 76]. These studies clearly refute previous notions that injected aluminum adjuvant nanoparticles remain localized at the injection site and only act on the immune system through some "depot effect."

The examples in mice and sheep have obvious relevance for human exposure to aluminum adjuvants, and the noted CNS pathologies are worth considering in the context of the development of age-related neurological disorders of all kinds.

In particular, the work on MMF and the in vivo models of the same [29, 30, 76] show that the bioaccumulation of aluminum in the CNS can occur at a very slow rate under many different conditions, especially by periodic vaccination with aluminum-adjuvanted vaccines.

Aluminum accumulation may be expected to be equally slow when the source is drinking water or food, and its deleterious eventual outcomes will be the result of cumulative body/brain burden and age. In the latter regard, there is evidence from older literature that aluminum in the brains of the elderly, of Alzheimer's disease patients, and of those with various forms of dementia is often associated with NFTs [61, 106–108, 136, 147]. The source of the CNS aluminum in these cases is not known and could be any of those mentioned in this section.

What will be obvious from a consideration of these data is that while aluminum has the potential to be both acutely toxic, as in DAE, and chronically toxic, as perhaps in Alzheimer's disease, the range of impacts on the CNS can be extremely varied, both in CNS area affected and the time course of any resulting pathology. In this regard, aluminum neurotoxicity is disseminated both spatially and temporally in a manner that may more closely resemble the typical phenotype of multiple sclerosis. What is equally clear is that aluminum has the capacity to impact the CNS at multiple levels of organization, from DNA all the way though to higher systems interactions [125].

From the preceding, one way to view aluminum neurotoxicity may be to consider it as a generally neurotoxic element with spatial variations in CNS subsystem impacts that are extremely diverse. In this view, the precise outcome may depend on a variety of intrinsic and extrinsic factors. Concerning the former, age, sex, and individual genetic polymorphisms and biochemistries (including the microbiome; see Scheperjans et al. [121]) are likely to be key players. Extrinsic factors include the type of aluminum compound, the amount of exposure, and the route of exposure (e.g., by food, water, intramuscular versus other types of injection, inhalation, etc.).

For all of these reasons, the toxicity of aluminum in the CNS appears to depend on a number of variables, which include both direct and indirect cellular mechanisms. In either case, factors include the form of aluminum complex, the size of the particles, the route of administration, and the dose. Dose itself may not be the major consideration [30]. In animal models, species and even strain may influence aluminum outcomes [29]. Finally, it should now be apparent that interactions with the immune system, to be discussed below, will determine, at least in part, the influence of the other factors.

The full range of CNS impacts of aluminum is shown in Table 4.2.

4.3.1 Aluminum-Triggered Genetic Alterations and Protein Expression Levels

An emerging area of study is that of "epigenetics" or the changes in gene expression regardless of the mutational state of the gene. Epigenetic modifications can occur in several ways. The first is when a stable but reversible alteration of gene function is mediated by histone modification, cytosine methylation, the binding of nuclear proteins to chromatin, or interactions among any of these elements. Such modification does not require, or generally involve, any changes in the DNA sequence itself.

A second way epigenetic modification can occur is through "epimutation" or a heritable change in gene expression that does not affect the DNA sequence. Instead, epimutation involves the silencing of a gene that is not normally silenced or, conversely, the activation of a gene that is not normally active. It is useful in this regard to consider the probability demonstrated in the literature that some factor, perhaps a toxin, can be the trigger of such epigenetic changes, whose net consequence is to cause some gene to under- or over-express downstream protein production. A recent example ties back to the discussion of aluminum toxicity and is based on older observations that aluminum can bind to and alter DNA [74].

The key point here is to illustrate what may serve as a new way of looking at the interaction between genes and toxins in that genes do not have to be modifiable in their DNA structure in order to be modified in their expression. The fact that some toxins, such as aluminum, can do so in the CNS may prove to be a factor in the impact of such toxins on neurological disease.

4.3.2 miRNA Alterations in Gene Expression

A less direct means of altering gene expression occurs in the impact that various other genes or molecules may have on the transcriptional machinery of the cell, notably transfer and messenger RNA. RNA transcriptional errors have been implicated in ALS and other neurological diseases [100, 135]. Gene expression is also affected by microRNA (miRNA), which can act to silence various gene expression patterns. Again, aluminum may be one of the contributors to this outcome. Changes in miRNA have been implicated in Alzheimer's disease, as one example [89]. In context to the aluminum-induced gene expression changes, the impact of aluminum on miRNA cannot be discounted.

Table 4.2 Aluminum's CNS impacts in animals and humans

Al's neurotoxic effects related to AD
Effects on memory, cognition, and psychomotor control
Significantly decreases cognitive and psychomotor performance in humans and animals
Impairs visuomotor coordination and long-term memory and increases sensitivity to flicker in humans and rats
Impairs memory and hippocampal long-term potentiation (LTP) in rats and rabbits in vivo (electrophysiological model of synaptic plasticity and learning)
Effects on neurotransmission and synaptic activity
Depresses the levels and activity of key neurotransmitters known to decline in AD in vivo: acetylcholine, serotonin, norepinephrine, dopamine, and glutamate
Reproduces hallmark cholinergic deficits observed in AD patients by impairing the activity of cholinergic synthetic and transport enzymes:
Impairs acetylcholinesterase activity
Reduces neural choline acetyltransferase
Inhibits choline transport in rat brain and in synaptosomes from the cortex and hippocampus
Attenuates acetylcholine levels in rabbit hippocampus and concomitantly induces a learning deficit
May cause acetylcholine deficit by acting upon muscarinic receptors and potentiating the negative feedback controlling acetylcholine release into the synaptic cleft
Inhibits neuronal glutamate-nitric oxide (NO)-cyclic GMP (cGMP) pathway necessary for LTP
Damages dendrites and synapses
Impairs the activity of key synaptosomal enzymes dependent on Na-K, Mg^{2+}, and Ca^{2+}
Inhibits glutamate, GABA, and serotonin uptake into synaptosomes
Impairs neurotransmission by disrupting post-receptor signal transduction mediated by the two principal G-protein regulated pathways: PLC and AC (see effects on G-proteins and Ca^{2+} homeostasis)
Inhibits dihydropteridine reductase, essential for the maintenance of tetrahydrobiopterin (BH4), a cofactor important in the synthesis and regulation of neurotransmitters
Impairs ATP-mediated regulation of ionotropic and metabotropic receptors – cholinergic, glutamatergic, and GABAergic
Interferes with receptor desensitization by increasing the stability of the metal-ATP receptor complex and causes prolonged receptor activity (by replacing Mg^{2+} from the metal site)
Effects on G-proteins and Ca^{2+} homeostasis
Alters IP and cAMP signaling cascades by interfering with G-proteins (as AlF), second messengers and second messenger/Ca^{2+} targets:
Potentiates agonist-stimulated cAMP production following chronic oral exposure in rats, by inhibiting the GTPase activity of the stimulatory G-protein (Gs), leading to prolonged activation of Gs after receptor stimulation and increased cyclic AMP production by AC
Increases cAMP levels by 30–70% in brains of adult and weanling rats
Inhibits muscarinic, adrenergic, and metabotropic receptor-stimulated IP3 accumulation by inhibiting Gq-dependent hydrolysis of PIP2 by PLC
Decreases IP3 in the hippocampus in rats following chronic oral administration
Inhibits PKC
Blocks the fast phase of voltage-dependent Ca^{2+} influx into synaptosomes

(continued)

Table 4.2 (continued)

Al's neurotoxic effects related to AD
Binds to CaM and interferes with numerous CaM-dependent phosphorylation/dephosphorylation reactions
Impairs Ca^{2+}/CaM-dependent LTP
May cause a prolonged elevation in intracellular Ca^{2+} levels by:
Interfering with desensitization of the N-methyl D-aspartate (NMDA) receptor channel
Delaying the closure of voltage-dependent Ca^{2+} channels
Blocking CaM-dependent Ca^{2+}/Mg^{2+}-ATPase responsible for extrusion of excess intracellular Ca^{2+}
Elicits a Ca^{2+}-dependent excitotoxic cascade by frequent stimulation of the NMDA receptor which may result in:
Persistent further activation of NMDA receptor by endogenous glutamate and exacerbation of glutamate excitotoxicity
Mitochondrial and ER Ca^{2+} store overload
Compromised neuronal energy levels
Erosion of synaptic plasticity
Increased susceptibility to apoptosis and accelerated neuronal loss
Perturbs neuronal Ca^{2+} homeostasis and inhibits mitochondrial respiration in a complex with amyloidogenic A peptide in a triple transgenic mouse model of AD
Metabolic and inflammatory effects
Inhibits utilization of glucose in the brain
Inhibits hexokinase and G6PD
Reduces glucose uptake by cortical synaptosomes
Alters Fe^{2+}/Fe^{3+} homeostasis and potentiates oxidative damage via Fenton chemistry
Alters membrane properties by:
Decreasing the content of acidic phospholipid classes: phosphatidylserine (PS), phosphatidylinositol (PI), and phosphatidic acid (PA) in rat brain myelin by 70%
Inducing the clustering of negatively charged phospholipids, thereby promoting phase separation and membrane rigidification and facilitating brain-specific LPO
Increases the permeability of the BBB by:
Increasing the rate of transmembrane diffusion
Selectively changing saturable transport systems
Facilitates glutamate transport across the BBB and potentiates glutamate excitotoxicity
Decreases antioxidant activity of SOD and catalase in the brain
Increases cerebellar levels of nitric oxide synthase (NOS)
Augments specific neuro-inflammatory and pro-apoptotic cascades by inducing transcription from a subset of HIF-1- and NF-B-dependent promoters (APP, IL-1 precursor, cPLA2, COX-2, and DAXX)
Activates microglia, exacerbates inflammation, and promotes degeneration of motor neurons
Nuclear effects
Binds to phosphonucleotides and increases the stability of DNA
Binds to linker histones, increases chromatin compaction, depresses transcription
Inhibits RNA polymerase activity
Reduces the expression of the key cytoskeletal proteins tubulin and actin

(continued)

Table 4.2 (continued)

Al's neurotoxic effects related to AD
Downregulates the expression of the light chain of the neuron-specific neurofilament (NFL) gene in 86% of surviving neurons in the superior temporal gyrus of AD patients
Upregulates well-known AD-related genes: amyloid precursor-like protein (APLP)-1 and APLP-2, tau, and APP, in human neuroblastoma cells when complexed with A, to a larger extent than other A-metal complexes (A-Zn, A-Cu, and A-Fe)
Upregulates HIF-1- and NF-B-dependent gene expression (see metabolic and inflammatory effects)
Effects on MTs, cytoskeleton, and NFT formation
Induces neurofibrillary degeneration in basal forebrain cholinergic neurons and cortical and hippocampal neurons and accumulates in NFT-bearing neurons
Causes neurite damage and synapse loss in hippocampal and cortical pyramidal neurons by disabling their capacity for MT assembly
Directly alters MT assembly by interfering with magnesium and GTP-dependent MT-polymerization mechanisms. Actively displaces magnesium from magnesium-binding sites on tubulin and promotes tubulin polymerization
Decreases the sensitivity of MTs to calcium-induced depolymerization and effectively disables the regulatory circuits that are set to maintain the sensitive dynamics between polymerization and depolymerization cycles of tubulin and, ultimately, impairs MT assembly
Inhibits axonal and dendritic transport mechanisms by depleting MTs
Induces cAMP-dependent protein kinase phosphorylation of MAPs and NFs in rats following chronic oral exposure and enhances the formation of insoluble NF aggregates. Al-induced hyperphosphorylated NFs are resistant to dephosphorylation and degradation by calcium-dependent proteases (calpain)
Promotes highly specific nonenzymatic phosphorylation of tau protein in vitro by catalyzing a covalent transfer of the entire triphosphate group from ATP to tau via O-linkage (cAMP-dependent protein kinase phosphorylation sites), at concentrations similar to those reported in AD brains
Induces tau phosphorylation and motor neuron degeneration in vivo (as a vaccine adjuvant)
Facilitates cross-linking of hyperphosphorylated tau in PHFs, stabilizes PHFs, and increases their resistance to proteolysis
Inhibits dephosphorylation of tau in synaptosomal cytosol fractions
Decreases levels of specific MAP isoforms
Effects on amyloidosis
Elevates APP expression and induces senile plaque deposition in 30% of patients subjected to chronic dialysis treatment
Elevates APP expression and promotes A deposition and amyloidosis in hippocampal and cortical pyramidal neurons in rats and mice following chronic oral exposure
Binds the amyloidogenic A peptide and perturbs its structure from a soluble-helical form to the insoluble random turn-sheet conformation at physiologically relevant concentrations. The neurotoxic A-sheet conformation may be reversed by the addition of a natural Al binder-silicic acid, a promising therapeutic agent for AD
Promotes the formation of amyloid fibrils in complex with ATP and induces their aggregation
Induces conformational changes in A and enhances its aggregation in vitro in cultured mouse cortical neurons, following chronic (50 M,>3 weeks) but not acute exposure (10–100 M, 1 week)

(continued)

Table 4.2 (continued)

Al's neurotoxic effects related to AD
Appears to be the most efficient cation in promoting A1-42 aggregation and potentiating A1-42 cellular toxicity in human neuroblastoma cells:
Induces a specific oligomeric state of A1–42 and by stabilizing this assembly markedly reduces cell viability and alters membrane structure, an effect not seen with other metal complexes (A1-42-Zn, A1-42-Cu, and A1-42-Fe) or A1-42 alone
Strongly enhances the spontaneous increase of A1-42 surface hydrophobicity (compared to A1-42 alone, A1-42-Zn, A1-42-Cu, and A1-42-Fe), converting the peptide into partially folded conformations
May promote amyloidosis by interfering with the muscarinic acetylcholine receptor-stimulated IP3/PLC-regulated production of the neuroprotective nonamyloidogenic s-APP:
As fluoroaluminate, blocks DAG/PKC-dependent budding of secretory vesicles containing APP from the trans-Golgi network (TGN), thus inhibiting APP redistribution toward the plasma membrane where it would undergo processing by secretase to produce s-APP
May inhibit IP3/Ca^{2+} – dependent production of s-APP
May inhibit PKC-dependent APP cleavage by secretase
Inhibits proteolytic degradation of A by cathepsin D

Adapted from Tomljenovic [139] which contains the literature citations for each Al-induced change.

4.4 Overview of Innate Versus Adaptive Immune Systems and Their Roles in CNS Development and Neurological Disease

There is now a growing body of evidence suggesting that the immune and nervous systems are uniquely interrelated, both in development and in mature function. Nowhere is this linkage clearer than in considerations of ASD. (Note, much of the following sections has been excerpted from [106].

The innate ("natural") immune system is a non-specific first line of defense against infectious diseases. It is composed of various cells and molecules that can recognize invading pathogens and consists of eosinophils, monocytes, macrophages, natural killer cells, dendritic cells, Toll-like receptors, and complement system mediators (for a general overview, see Janeway et al. [70]). In this system, the first response to a given pathogen is relatively slow, but it becomes more rapid with a secondary exposure to the same entity. In contrast, the adaptive immune system is specifically directed against invading pathogens. It contains highly specialized cells such as T (thymus-derived) and B lymphocyte (bone marrow-derived) cells, generating, respectively, cellular and humoral types of immune response. T cells, also termed T-helper, T4, or CD4 cells, are white blood cells that are essential for the adaptive immune response. "CD4" refers to a glycoprotein (cluster of differentiation 4) found on the surface of T cells and other cell types (e.g., monocytes, macrophages, and dendritic cells). T-helper cells do not themselves destroy invading pathogens as they have no phagocytic or cytotoxic capabilities, but they enable other cells such as CD8 killer cells to do so. Two types of T-helper cell are recognized,

Th1 and Th2, each designed to eliminate different types of pathogen. Th1 cells produce interferon γ and act to activate the bactericidal actions of macrophages and induce B cells to make complement-fixing antibodies. These responses are the basis of cell-mediated immunity.

The Th2 response involves the release of interleukin 5 (IL-5), acting to induce eosinophils to clear parasites. Th2 also produces IL-4, which facilitates B-cell isotype switching. In general, Th1 responses are usually directed against intracellular pathogens (viruses and bacteria), while Th2 responses act against extracellular bacteria, other pathogenic parasites, and toxins.

A second crucial aspect of the adaptive immune system, particularly in response to future pathogen responses, is the production of antibodies. Antibodies are immunoglobulins (Igs): large Y-shaped proteins produced by plasma cells of which there are a variety of isotypes each with particular actions and localizations of such action.

When describing features of the innate immune system, it is necessary to consider the role of the "inflammasome." The inflammasome is an intracellular, multiprotein complex that controls the activation of proinflammatory caspases, primarily caspase-1. The complex generally has three main components: a cytosolic pattern-recognition receptor known as the nucleotide-binding oligomerization domain (NOD)-like receptor (NLR), the enzyme caspase-1 (part of the apoptosis pathway), and an adaptor protein known as apoptosis-associated speck-like protein (ASC), which facilitates the interaction between the NLR and caspase-1 (see review by Walsh et al. [148]). The NLR subfamilies include NLRP3, the best studied of this group.

The NLRP3 inflammasome is activated by various stimuli, including pathogenic signals (e.g., bacterial, fungal, viral) [36, 68], endogenous danger signals (adenosine triphosphate (ATP), Aβ, uric acid crystals) [58, 90, 91], and environmental microparticles (e.g., silica crystals, aluminum salts) [65]. The latter are of obvious importance in consideration of the impact of aluminum salts used as adjuvants that may also gain ingress into the CNS.

NLRP3 activation is a two-step process. A first signal, such as the presence of microbial Toll-like receptor ligands, primes cells by producing pro-IL-1β expression. A second signal, such as ATP, activates caspase-1 and leads it to process pro-IL-1β and pro-IL-18 [58, 90, 142]. The activation of NLRP3 is not completely understood, but three upstream mechanisms of activation have been proposed. These are ion fluxes (K+ and other ions) [110], mitochondrial-derived reactive oxygen species [160], and phagosome destabilization and the release of lysosomal enzymes (cathepsins) that digest proteins after cell death [24, 64].

The effects of NLRP3 inflammasome activation within the CNS remain unknown in many cases, but recent evidence suggests it has a role in neurological diseases and, as already mentioned, in the context of adjuvant aluminum salts.

4.4.1 HPA–Immune System Interactions in Development and Disease

IL-1β, the key proinflammatory cytokine, is released following NLPR3 inflammasome activation by aluminum adjuvants and exhibits multifactorial effects on the immune system [37, 80, 81]. IL-1β is also known to activate neurons in the central nucleus of the amygdala [17]. This nucleus plays a major role in the HPA axis response to systemic immune stimulation [155]. Abnormalities in the amygdala [62, 97] and alterations in cortisol levels indicative of a dysfunctional HPA axis are common in ASD children and may, in part, serve to explain the limited abilities of these children to react adequately to their social environment, as well as their tendency toward enhanced anxiety behaviors [59, 113].

The HPA axis is not only crucial for regulating a broad array of psychological stress responses [31, 56, 57, 71] but also regulates neuro-immune stress arising from exposure to bacterial and/or viral stimuli.

From the preceding, it is clear that the HPA axis is one of the major pathways by which the CNS regulates the immune system [38, 39, 41, 98, 154]. Alterations in HPA axis regulation can lead either to excessive immune activation, and hence inflammatory and autoimmune disorders, or to excessive immune suppression and thus increased susceptibility to infectious diseases.

In this context, it is notable that many autoimmune/inflammatory conditions have been consistently linked to adjuvant administration and/or repetitive immunizations with antigenic components, including aluminum adjuvants [88, 113, 125, 141, 143].

Cortisol, the main glucocorticoid hormone product of HPA activity, appears to have a crucial role in priming microglia toward a hyperactive state and thus a role in neurodegeneration by inducing the M1 phenotype [8]. In adult rats, prior sensitization of the microglia by cortisol potentiates the proinflammatory response to a peripheral immune challenge by lipopolysaccharide (LPS) and significantly augments the production of the inflammatory cytokines IL-1β, IL-6, and TNF-α in the brain [47].

Glutamate is the major excitatory neurotransmitter in the mammalian brain and is therefore crucial for normal brain development and function [55, 72]. However, excessive glutamate release is deleterious to neuronal viability and is thought to play a role in the pathophysiology of neurological diseases and neuropsychiatric disorders, including ASD [13, 55]. In regard to ASD, children and adults with the disorder typically display higher serum levels of glutamate [128, 129], as well as a specifically higher concentration of glutamate/glutamine in the amygdala and hippocampus [114].

The higher levels of glutamate in ASD children find a direct correlate with the levels of glutamatergic receptors: at 2 years of age, the developing human brain contains more synaptic glutamate receptors than at birth, but the number of these receptors progressively declines over the next decade. The immature brain is thus likely to be more susceptible to excitotoxic insults than that of a young adult [72].

At the other end of the age spectrum, receptor subunit composition for various glutamate receptor subtypes also changes during life [111], which may make the aged brain more susceptible to excitotoxic insults than that of younger adults. Thus, the dynamics of glutamate levels and glutamate receptor characteristics across the life span makes neuronal vulnerability more pronounced in early and later life, albeit in different ways. In turn, this complex response pattern reflects the underlying complexity contributed by neural–immune–HPA interactions.

4.4.2 Autoimmunity

Briefly stated, autoimmune disorders arise when an individual's own immune system generates antibodies that attack healthy tissues rather than the invading pathogens.

Autoimmune reactions can also cause the abnormal growth of tissues and a variety of dysfunctional states. Examples of organ systems that can be affected include blood cells and vessels, connective tissues and joints, skin and muscles, the endocrine system, and, of particular interest in what follows, the CNS.

Close to 100 autoimmune disorders are now recognized, with more added to the list every year. Well-known autoimmune disorders include systemic lupus erythematosus (SLE), celiac disease, rheumatoid arthritis, type 1 diabetes, and a host of other lesser-known disorders. In the CNS, autoimmune disorders include multiple sclerosis, Guillain–Barré syndrome, and myasthenia gravis.

Autoimmune disorders can have multisystem impacts, and individuals can have more than one such disorder at the same time. Likely examples of multisystem syndromes include fibromyalgia, chronic fatigue syndrome, and the emerging syndrome termed "autoimmune syndrome/inflammatory syndrome induced by adjuvants" ASIA. Gulf War syndrome, which in many cases includes clearly negative impacts on the CNS [32], likely also reflects a multisystem autoimmune disorder of the ASIA type. As cited above, MMF is triggered by aluminum adjuvants and leads to clear changes in cortical function in the form of MCI. The observation that aluminum salts can themselves be antigenic lends support to the notion that MMF may have autoimmune as well as inflammatory features [51] and places it firmly within the ASIA spectrum of disorders.

The link between abnormal immune system function and ASD is illustrated in Table 4.3.

It should be mentioned that the potential link between the various autoimmune/inflammatory CNS disorders and adjuvants, particularly aluminum adjuvants in vaccines, has led some investigators to question whether these disorders actually exist [60]. Such views sometimes appear to reflect more the perceived need to provide continued public assurance about vaccine safety, rather than any actual reservations about whether such disorders are aluminum-induced and/or autoimmune in nature.

Table 4.3 Immune system role in ASD

Types of abnormalities	Type of immune stimuli/time of stimulation	Species	Outcome	Autism
Neurobehavioral	Poly I:C/early postnatal	Mouse, rat	Deficits in social interaction, increased anxiety [67, 77]	Impaired social skills, increased anxiety and stereotypic behavior [138]
	LPS/early postnatal	Rat	Altered responses to novel situations (i.e., reluctance to explore a novel object) [133]	Anxiety to novel situations, preference for routine [71]
	Poly I:C/early postnatal	Mouse	Cognitive dysfunction (i.e., memory deficits [67]	Cognitive dysfunction and mental retardation [46, 99]
Neuroanatomical	Poly I:C/prenatal	Mouse	Compromised neurogenesis and abnormal formation of the cerebral cortex [132]	Abnormal neuronal morphology and cytoarchitecture of cerebral cortex [62]
	Complete US pediatric vaccine schedule/ postnatal, according to schedule	Monkey	Failure to undergo normal maturational changes in amygdala volume [63]	Impaired amygdala development [62, 97]
Neurochemical	Poly I:C/early postnatal	Mouse	Increased extracellular glutamate in the hippocampus [67]	Increased glutamate in the amygdala-hippocampal region [114]
	LPS/early postnatal	Rat	Increased seizure susceptibility [48]	Increased seizures and epilepsy [7, 144]
Immune	LPS/early postnatal	Rat	Abnormal cytokine profiles [134]	Abnormal cytokine profiles [5, 6, 94, 104, 145]
	Al-adjuvant/ early adulthood	Mouse	Increased astrocyte and microglia reactivity [11, 12]	Increased astrocyte and microglia reactivity [5, 6, 94, 104, 145]
	LPS/early postnatal	Rat	Exacerbation of inflammatory conditions [134]	Immune hypersensitivity [33]

Shared aspects between autism and abnormal neurobehavioral, neuroanatomical, neurochemical, and immune system outcomes resulting from repeated peripheral immune stimulation (From Ref. [122])

Poly I:C polyriboinosinic–polyribocytidilic acid, a synthetic analogue of double-stranded RNA (viral antigen), *LPS E. coli* lipopolysaccharide

The precise mechanisms of action of aluminum adjuvants are still being resolved almost 90 years after their introduction [44]. Whatever else one wishes to say about the role of aluminum adjuvants in autoimmune disorders, aluminum is distinctly not inert, nor are the cumulative amounts received necessarily trivial for CNS health, as detailed above. Indeed, as discussed in the present section, the interactions between the immune and nervous systems virtually ensure that adjuvant aluminum will impact both, even if the intent is only to modify the former.

Autoimmune disorders often display differences based on sex. For example, multiple sclerosis [103], MMF [115], and ASIA in general [159] appear much more often in women than in men (3.2:1; 7:3; 7:3, respectively), a point of some relevance to ASD which mostly occurs in males. Many autoimmune disorders also show an age window, that is, a particular range of ages during which they are most likely to arise. The underlying reasons for both of these observations are unclear.

4.4.3 Aluminum and Failed Biosemiosis

Because the nervous system utterly depends on signaling from the gene (or any part of the DNA that induces protein production) up to neuronal and neural systems outputs, anything that degrades biological signaling, termed "biosemiosis," may be highly deleterious.

In this regard, aluminum, with its demonstrated potential to impact the various levels of organization, may be one of the more destructive toxins to the CNS from the perspective of multilevel biosemiosis. Insofar as aluminum can alter DNA and RNA, such actions will lead to altered proteins which, in turn, will impact cellular function. Moving upward in levels in the CNS, dysfunctional cells cannot help but alter neural circuit function, neural systems function, and, ultimately, behavior. In this manner, aluminum alone may induce a "multiple-hit" outcome in the CNS on its own, making it perhaps uniquely toxic among the various substances known to negatively impact the CNS [125].

4.4.4 Aluminum's Role in Immune System Signaling Errors with a Focus on ASD

Which factors might serve as triggers to abnormal immune function as it relates to the CNS in development or in adulthood? The above material details much of the information on aluminum toxicity in the context of neurological disease, including developmental disorders such as ASD. The maternal immune activation (MIA) studies cited below further bolster this notion given aluminum's clearly demonstrated adjuvant, and thus immune-stimulating, actions.

As already noted, however, the subject of aluminum involvement in ASD remains highly controversial. In part, some of this controversy may arise from addressing developmental disorders in relation to a possible causal impact of this element. As also noted above, a certain part of the medical community has discounted any deleterious role for aluminum for human health in general. More specifically, hesitation to accept a role for aluminum in ASD may arise because it is virtually impossible to avoid considering one major source of aluminum exposure: aluminum-adjuvanted pediatric vaccines.

So explosive is the potential impact of such a linkage that it often forces investigators to assert that aluminum could not be involved in ASD at all, in spite of the rather large literature on aluminum neurotoxicity, in part cited above. This position appears primarily to be an attempt to avoid any discussion of vaccine safety. From a strictly scientific perspective, albeit not necessarily from that of those concerned with reassuring the public about vaccine safety per se, this position would appear to be problematic.

In spite of such reservations, the available literature clearly shows that the neurotoxicity of aluminum in the CNS manifests itself in symptoms such as deficits in learning, memory, concentration, speech, and psychomotor control, as well as increased seizure activity and altered behavior (i.e., confusion, anxiety, repetitive behaviors, and sleep disturbances) [139]. All of these are features of the overall spectrum of disorders included in ASD.

In regard to aluminum adjuvants, the prolonged hyperactivation of the immune system and chronic inflammation triggered by repeated exposure, combined with the unexpectedly long persistence of such adjuvants in the human body, are thought to be principal factors underlying the toxicity of these compounds. In regard to the latter point, one reason aluminum salts such as the hydroxide are so effective as adjuvants is the relative inability of the body to excrete or degrade them in comparison to aluminum derived through dietary exposure. This clearly demonstrated point from the literature is often overlooked or ignored when assessing vaccine safety, sometimes leading to spurious comparisons between the amounts of aluminum found in a standard vaccine and those in various food products or in the diet overall.

Over the last decade, in vivo studies in animal models and humans have indicated that aluminum adjuvants have an intrinsic ability to induce adverse neurological and immune-inflammatory outcomes [28, 82, 105, 109]. Some of these studies have led to the description of the ASIA syndrome, which is known to comprise a wide spectrum of adjuvant-induced conditions characterized by a mis-regulated immune response [94, 130].

The ability of aluminum adjuvants to cross the blood–brain and blood–cerebrospinal fluid barriers [76, 88, 124] may in part explain the adverse manifestations following some vaccines which tend to be neurological in nature, with an underlying immunoinflammatory component [26, 131, 159]. Thus, as cited above, aluminum's impact on the CNS is likely a component of the bidirectional aspects of CNS–immune system interactions.

The data for MMF cited here may also suggest that some forms of neurological or immune system dysfunction could also arise in children, particularly considering

the potential body burden of aluminum that the children can accumulate. While an adult MMF patient may have received up to 17 vaccines in the 10 years prior to diagnosis, the average child in the United States following the Centers for Disease Control and Prevention (CDC)'s vaccination schedule will receive the same number of aluminum-adjuvanted vaccines in their first 18 months of life [140, 141]. Given that early postnatal life in humans is a period of intense neurological development, anything that has the potential to interfere with such development is going to place the system as risk.

It should be stressed in this context that toxins other than aluminum have also been proposed to be involved in ASD [33]. This possibility does not diminish the potential impact of aluminum itself, however. The ability of aluminum to adversely affect both the immune and the nervous system in an interactive manner makes it a strong candidate risk factor for triggering developmental disorders such as ASD in which the two principal features are precisely those of neurological and immune system signaling dysfunctions.

It should be clear from the above that the etiology of ASD is not a simple process involving only genetic factors, but rather involves a multiple-hit type of etiology in which both immune and nervous system interactions driven by a combination of genetic susceptibilities and environmental agents play important roles. This notion is not particularly surprising given the existing literature on neurodegenerative diseases associated with aging (e.g., AD, PD, and ALS), which often comes to many of the same conclusions.

4.4.5 Pathogen and Aluminum Activation of the Immune System in Relation to the CNS

Repeated administration of bacterial and viral antigenic protein fragments, many of which are adsorbed to adjuvant aluminum salts, is clearly analogous both in nature and timing to peripheral immune stimulation with microbial mimetics in experimental animals during early periods of developmental vulnerability. If administered during these periods (including early postnatal life), such potent immune stimuli can not only produce adverse neurodevelopmental outcomes in these animals but can also permanently impair immune responses to subsequent immune challenges later in life [14, 49]. These MIA outcomes can have profound effects, some of which are linked to ASD.

Many cytokines induced as part of an immune response, including those arising from adjuvants, can act as "endogenous pyrogens"; that is, they can induce a rapid-onset fever by acting directly on the hypothalamus, without the need for the formation of another cytokine (i.e., IL-1β, IL-6, TNF-α) [9, 10, 27, 34]. While transient fever is an essential component of the early immune response to infection, a prolonged febrile response is a hallmark of many inflammatory and autoimmune diseases [34].

Fever-promoting cytokines produced in peripheral tissues by immune stimulation can enter the brain by way of the circumventricular organs (CVOs) [34]. CVOs

are structures in the brain with an extensive vasculature and are among the few sites devoid of protection by the blood–brain barrier. They provide one link between the CNS and peripheral blood flow and thus are an integral part of neuroendocrine function.

The absence of a blood–brain barrier to CVO molecule release allows the CVOs to provide an alternative means for the release of hormones and various peptides from the CNS into peripheral circulation. As well, the structural connections now demonstrated between the lymphatic system and the CNS only add to the potential for immune–CNS bidirectional ingress [87]. In this context, persistent inflammation of the CNS appears to play a prominent role in neurodevelopmental and neurodegenerative disorders [2, 89, 104, 145].

4.5 Summary and Final Considerations

The data cited in the above sections clearly shows that aluminum, far from being either inert or safe, is actually "insidiously unsafe" [76] in any of its manifestations or routes of ingress into the bodies of humans or animals [125]. In adult humans or animals, the impacts include those of various organ systems, particularly the CNS and immune system, and can lead to a variety of multisystem disorders. In children, especially early in CNS development, exposure to aluminum from various sources, possibly significantly from vaccines containing aluminum adjuvants, may have profound deleterious consequences. One of these consequences may be ASD.

We live in a period described by some authors as the "age of aluminum." Aluminum, once relatively inaccessible in the biosphere, has become ubiquitous. Given the dangers that elemental aluminum poses to the various organ systems, it would behoove us to limit our exposures to this toxic element in food, water, cosmetics, and various medicinal products, including in vaccines.

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