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Review Article

Fluoride, aluminum, and aluminofluoride complexes in pathogenesis of the autism spectrum disorders: A possible role of immunoexcitotoxicity

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ABSTRACT

Autism spectrum disorders (ASD) are characterized by impairments in social interaction and communication along with stereotyped patterns of behaviors. Over the past several decades, the prevalence of ASD has increased dramatically. ASD are highly multifactorial, with many risk factors acting together. Our review suggests that most risk factors are connected to immunoexcitotoxicity. Fluoride exposure is common as a result of the artificial fluoridation of drinking water and a dramatic increase in the volume of man-made industrial fluoride compounds released into the environment. Human exposure to environmental aluminum is extensive and appears to be growing. The long-term fluoride and aluminum burden have several health effects with a striking resemblance to the ASD. Moreover, both fluoride and aluminum interfere with a number of glycolytic enzymes, resulting in a significant suppression of cellular energy production. The synergistic interactions of fluoride and aluminum increase the potential neurotoxic effect particularly in children. Aluminofluoride complexes have effects on cell signaling, neurodevelopment, and neuronal function. We suggest that the burden with these new ecotoxicological factors could contribute to an alarming increase in the prevalence of ASD.

Introduction

The prevalence of autism spectrum disorder (ASD) has risen dramatically since the surveillance of the Centers for Disease Control and Prevention (CDC) in 2000. About one percent of the world population has ASD and it is the fastest-growing developmental disability (Blaylock and Strunecka, 2009). A recent CDC surveillance study identified 1 in 68 children (1 in 42 boys and 1 in 189 girls) as having ASD in the USA. The

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etiology of ASD remain an unsolved puzzle to scientists, physicians, pediatricians, psychiatrists, and pharmacologists. Of great concern is that no central mechanism has been proposed to explain the various clinical presentations of ASD and no evidence-based therapy has been offered. The heterogeneity of pathophysiological, histological, neurological, biochemical, clinical, and behavioral symptoms provide us little reason to assume that there is one cause of ASD pathogenesis, *e.g.* genetic. While aluminum (Al^{3+}) has been cited among the possible culprits of ASD, fluoride is rarely considered. We suggest that multiple environmental risk factors may cause the dysregulation of immune-glutamate pathways in ASD (Blaylock and Strunecka, 2009; Strunecka et al., 2010). Blaylock (2004) coined the term immunoexcitotoxicity as a possible central mechanism to describe the interaction between immune activation and excitotoxicity; an interaction common to a great number of neurological disorders. A careful review of known environmental and pathological links to ASD indicates that most, if not all, are connected to the immunoexcitotoxic process. There is compelling evidence from a multitude of studies indicating that environmental and food borne substances as well as excitotoxins, such as fluoride, aluminum, mercury, glutamate and aspartate, can elevate blood and brain glutamate to levels known to cause neurodegeneration, brain inflammation, and alterations in the developing brain.

In the human condition we most often see a tremendous number of variables at play. Humans eat a wide variety of both natural foods and highly processed foods that contain a number of artificially created chemicals. In addition, they are breathing an atmosphere that is likewise significantly contaminated by a great number of pollutants, both artificially created and naturally occurring. These contaminants are not static but can vary considerably from day to day. Two of the most common contaminants of foods and water include aluminum and fluoride. In the modern world it is virtually impossible to avoid these two chemicals, usually present as a variety of compounds. Therefore, as pointed out by Strunecka et al. (2002), one must consider interactions between these two highly reactive substances when reviewing such studies. Chris Exley, for example, has pointed out that because of the ubiquitous nature of aluminum in our environment, it is reasonable to assume that aluminum is present in every chemical and physical compartment of the body (Exley, 2014). Like aluminum, fluoride is also a ubiquitous compound found in many soils, incorporated within edible plant components, in drinking water (both naturally and added) and is released into the atmosphere by several industries. Fluoride is now used in the manufacture of a growing number of pharmaceutical drugs, pesticides, teflon coatings and other products used by a great number of people. Fluoride is known to accumulate in teeth (as dental fluorosis). The incidence of dental fluorosis has increased dramatically in the United States, going from 10% of children in 1950 to 41% during the period 1999 through 2004, indicating a dramatic increase in ingestion of fluoride containing products and foods (Beltrán-Aguilar et al., 2010). The main sources appear to be through drinking water, fruit drinks, black tea, and fluoride dental products. Several studies have shown that fluoride has access to most compartments of the human body and can be retained in many tissues for a considerable amount of time.

The chemical interaction of aluminum and fluoride can occur in the aquatic environment or within the biological system, as conditions may dictate. This interaction occurs rapidly when the two elements come in contact, forming an aluminofluoride complex (AlF_x). Vargas et al. (2005) reported in their study of autistic persons from age 5–44 year widespread microglial and astrocytic activation with the most intense activity being within the cerebellum. Microglia are the brain's primary immune cells. Both aluminum and fluoride can activate microglia. Astrocytes are the major site of storage and generation of glutamate, and possibly cytokines. Microglia, as well, contribute considerable levels of both pro-inflammatory cytokines and excitotoxins upon activation. Consistent with excitotoxicity is the finding of elevated levels of reactive oxygen species, reactive nitrogen species, and lipid peroxidation products in the brain, following fluoride exposure, both *in vitro* and *in vivo*. Also of interest is the finding of elevation in nitric oxide *via* induced nitric oxide synthase, again a critical component of excitotoxicity. The interactions between excitotoxins, inflammatory cytokines, and disruption of neuronal calcium homeostasis can result in brain changes suggestive of the pathological findings in cases of ASD. A complete loss of Purkinje cells in cerebellum of autistic persons was observed. Because Purkinje cells are involved in motor coordination, working memory and learning, the loss of these cells are likely to cause symptoms defining behavioral parameters of ASD (for a review see Strunecka et al., 2010).

The potential role of fluoride in the ASD pathophysiology

It is remarkable that fluoride is not recognized as a major causative candidate for consideration in the autism epidemic in the USA. However, exposure to fluoride among infants is a widespread problem in most major American cities. The investigation of the Environmental Working Group of the Fluoride Action Network found that up to 60% of formula-fed babies in US cities were exceeding the upper tolerable limit for fluoride. Using fluoridated water, a bottle-fed baby will receive up to 250 times more fluoride than from the mother's milk (Blaylock and Strunecka, 2009).

Substantial percentages of autistic patients display peripheral markers of mitochondrial energy metabolism dysfunction, such as elevated lactate and alanine levels in blood and serum carnitine deficiency (Strunecka et al., 2010). Lactate, the product of anaerobic glucose metabolism in the cytoplasm, accumulates when aerobic metabolism in mitochondria is impaired. Metabolic and mitochondrial defects may have toxic effects on brain cells, causing neuronal loss and altered modulation of neurotransmission systems. Depletion of cellular energy levels increases the vulnerability toward excitotoxins, leading to cell death.

Numerous studies have been published, which have raised the level of concern about the impacts of increasing fluoride exposure on the brain. These studies further highlight that it is not just the teeth, but the brain, that may be impacted by too much fluoride during development. Mullenix et al. (1995) compared behavior, body weight, plasma, and brain fluoride levels after fluoride exposures during late gestation, at weaning

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or in adults. Rats exposed prenatally had dispersed behaviors typical of hyperactivity, whereas rats exposed as adults displayed behavior-specific changes typical of cognitive deficits.

Reduction of children's intelligence and various psychiatric symptoms, such as memory impairment and difficulties with concentration, were reported when exposed to higher levels of fluoride. Several studies appeared from China, which indicated a lowering of IQ in children associated with fluoride exposure. Elevated fluoride content was found in embryonic brain tissues obtained from required abortions in areas where fluorosis was prevalent. These studies showed poor differentiation of brain nerve cells and delayed brain development (for a review see Strunecka et al., 2007). The fetal blood brain barrier is immature and readily permeable to fluoride. Fluoride may belong to the class of developmental neurotoxicants such as arsenic, lead, and mercury. The effects on individuals indicated that for each milligram increase of fluoride in urine, a decrease of 1.7 point in full IQ might be expected. These results indicated that chronic fluoride overload in the course of intrauterine fetal life may produce certain harmful effects on the developing brain of the fetus. The endocrine glands such as the thyroid and the pineal gland, are extremely sensitive to fluoride. It is already widely known that fluoride accumulates in the human pineal gland (Luke, 2001).

Alterations in metabolites of methionine–homocysteine cycle have been studied in details in ASD and provide a basis for the recommendation of vitamins B_6, folic acid (vitamin B_9), and vitamin B_{12} for the therapy. Homocysteine is a potent excitatory neurotransmitter that binds to glutamate NMDA receptors and leads to oxidative stress, calcium influx, and cellular apoptosis. Fluoride enters the cascade and attaches to the S-adenosyl homocysteine. All subsequent metabolites that follow become fluoridated, up to and including taurine. Fluoridated homocysteine is more likely than regular plain homocysteine to create injury. This suggests that ASD could be induced, or at least exacerbated, by fluoride exposure (for a review see Strunecka et al., 2010).

The role of aluminum in the excitotoxicity and ASD

Aluminum (Al^{3+}) has been discussed by several authors among the possible culprits of ASD (Tomljenovic and Shaw, 2011, 2013). Despite the abundance of aluminum in nature, it has no biological function in humans. Many investigations show that aluminum can elicit impairment of development and immunity, it acts as a hormonal disruptor, neurotoxin, and affects cognition and behavior. Al^{3+} is an experimentally demonstrated neurotoxin whose ability to impact the human nervous system has been known for decades. Sharma and Mishra (2006), using Wistar rats fed oral doses of aluminum chloride during gestation and post-partum. They found induced oxidative stress in the mother's brain as well as the brain of the fetus and suckling mice, along with a decrease in brain reduced glutathione, glutathione reductase and glutathione peroxidase, catalase, superoxide dismutase and acetyl cholinesterase.

Aluminum is considered to be the main immune stimulant in vaccine adjuvants. In an extensive review, Tomljenovic and Shaw (2011) pointed out that 18 aluminum-containing adjuvanted vaccines are included on the current pediatric vaccine schedule. In this study they found that (1) children from countries with the highest ASD incidence appear to have the highest exposure to aluminum from vaccines; (2) the increase in exposure to aluminum adjuvants significantly correlates with increase ASD in the US over the last two decades; (3) a significant correlation exist between the amounts of aluminum administered to preschool children and the current prevalence of ASD in seven Western countries, particularly at 3–4 months of age. The data satisfied Hill's criteria for causation.

When considering the effects of aluminum from vaccines, one must also consider the total body burden of aluminum from other sources. A number of studies have shown that the intake of aluminum compounds from foods varies greatly. A recent review of 30 infant formulas found that all contained aluminum and a number had concentrations far in excess of safety standards for oral consumption (Chuchu et al., 2013). In addition, parenteral solutions also contain aluminum. Impaired renal function as seen in infants and many elderly, greatly enhances the accumulation of aluminum in the body.

Compelling evidence indicates that elevation in maternal cytokines, especially IL-6 levels, during the last trimester of pregnancy is the causative factor for the dramatic elevation in autism and schizophrenia seen with maternal immune stimulation during this period of pregnancy (Parker-Athill and Tan, 2010; Bauman et al., 2014; Smith et al., 2007). Aluminum has been shown to selectively elevated IL-6 levels in aluminum fed animals (Viezeliene et al., 2013). Other studies have shown that peripheral immune stimulation early in the postnatal period results in a release of pro-inflammatory cytokines (IL-1ß, Il-6, IL-23) as well as excitotoxic levels of excitatory amino acids (glutamate, aspartate and quinolinic acid), which disrupts neurodevelopment and results in neurodegeneration (Ibi et al., 2009; Du et al., 2011). A large number of other immunoexcitotoxic induced behaviors are associated with both repetitive systemic immune stimulation and autism, such as anxiety, seizures and cognitive impairment (Frombonne, 1999; Danzer and Kelley, 2007; Blaylock and Strunecka, 2009; Blaylock, 2012). As few as two injections of aluminum adjuvants in vaccine relevant doses was found to be sufficient to cause dramatic activation of brain microglia and astrocytes that lasted up to 6 months post-injection (Shaw and Petrik, 2009). Microglial priming can occur following an initial systemic immune stimulus, either from natural infections or vaccine injection. A repeated immune stimulus within a few weeks to months can stimulate these primed microglia toward full activation, which in this case produces much higher levels of pro-inflammatory cytokines and possibly higher excitotoxin release (Perry and Holmes, 2014).

As a powerful immune activating element, aluminum can act both as the priming agent and the activation agent of immunoexcitotoxicity. This can occur with environmental exposure to excess aluminum, as well as injection by vaccination. The major difference is that ingested aluminum is very poorly absorbed, whereas injected aluminum is completely absorbed and distributed throughout the body, including the brain (Redhead et al., 1992; Flarend et al., 1997). Gherardi et al. (2015) have demonstrated accumulation of

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aluminum from adjuvated vaccines not only in regional lymph nodes, but also in the brain for prolonged periods. As a post-mitotic organ, neurons and glia are especially vulnerable to aluminum toxicity and accumulation. An emerging condition related to vaccine aluminum adjuvants, macrophagic myofasciitis, has been described which also includes a long-term neurodegenerative disorder and chronic cognitive dysfunction (Gherardi et al., 1998; Couette et al., 2009; Rigolet et al., 2014). In a study of the fate of injected aluminum adjuvants into muscle, researchers found that the aluminum particles were taken up mostly by microglia. MCP-1/CCL2, a chemokine released from microglia upon activation, appears to be the main attractant for transfer of aluminum from the periphery to the brain (Khan et al., 2013; Cadusseau et al., 2014).

With the demonstrated widespread accumulation of aluminum in the brain and spinal cord following aluminum exposure, combined with the immune stimulating effects of these aluminum compounds, all the conditions for an intense and prolonged activation of brain inflammation are present following systemic aluminum exposure or other forms of systemic immune activation. Aluminum-treated mice showed significantly increased apoptosis of motor neurons and increases in reactive astrocytes and microglial proliferation within the spinal cord and cortex (Shaw and Petrik, 2009). A number of brain conditions can act as a stimulus for microglial priming and subsequent activation upon systemic immune activation. This can include latent infection in the central nervous system (herpes simplex, cytomegalovirus), congenital brain lesions, and priming of microglial from repetitive minor brain traumas (Blaylock and Maroon, 2011).

Aluminofluoride complexes

The synergistic action of fluoride and Al^{3+} has an important implication for ASD pathology. Al^{3+} in micromolar concentrations avidly binds with fluoride to form aluminofluoride complexes (AlF_x) (Strunecka and Patocka, 1999; Strunecka et al., 2002, 2007). AlF_x has a potency that allows it to activate hundreds of G protein-coupled receptors (GPCRs). Moreover, the effects of AlF_x are amplified by processes of signal transduction. The principle of amplification of the initial signal during its conversion into a functional response has been a widely accepted tenet in cell physiology. This means that the effects of AlF_x result in pathophysiological consequences at several times lower concentrations than fluoride acting alone. It is evident that AlF_x is a molecule giving a false message (Strunecka et al., 2012). Such mechanism could explain the emergence phenomena in the pathogenesis of ASD on the molecular and cell level. Signaling disorders represent a major cause for the etiopathology of ASD. A number of studies have shown that AlF_x can affect learning and behavior, and induce a loss of cerebrovascular integrity both in experimental animals and humans.

Mullenix et al. (1995) demonstrated that the presence of fluoride enhances aluminum entry into the rat brain. Toxicological potential of fluoride is also markedly increased in the presence of trace amounts of aluminum. Varner et al. (1998) observed that Al^{3+}-induced neural degeneration in rats is greatly enhanced when the animals were fed low doses of fluoride. The presence of fluoride caused more Al^{3+} to cross the blood brain barrier and be deposited in the brains of rats. In their study using aluminum fluoride and sodium fluoride, Varner et al. found damage in the superficial layers of the cortex, amygdala, and cerebellum – all areas endowed with glutamate receptors. These authors described a loss of Purkinje cells with chronic fluoride exposure, a cell type containing abundant glutamate receptors. A growing number of studies have shown that inflammatory cytokines and chemokines can markedly enhance excitotoxicity. Moreover, research by Khan et al. (2013) and Cadusseau et al. (2014) shows that chemokines help to transport Al^{3+} to the brain. Microglia also contain numerous GPCRs, which can be affected by AlF_x and we know that they play an essential role in the development of the brain.

Some symptoms of ASD such as the sleep problems and the early onset of puberty suggest abnormalities in melatonin physiology and dysfunctions of the pineal gland (Strunecka et al., 2007, 2010). Many studies indicate clearly that nocturnal production of melatonin is reduced in ASD. Children with the lowest melatonin production had the most neurobehavioral problems. While melatonin is suggested for the therapy of autistic children, we recommend sleeping in a dark room. Melatonin is responsible for regulating numerous life processes, including development, immune system function, and oxidative stress. Melatonin has been shown to increase the levels of several of the antioxidant enzymes in the brain among a host of other physiologic and biochemical effects. Melatonin has a gamut of actions in human body. The pineal gland, represented by melatonin, is truly a ''regulator of regulators''.

A decrease of glutathione, a major intracellular antioxidant, is one of the best documented biochemical changes in autistic children. When combined with reduced mitochondrial energy production and reduced secretion of melatonin, one can reasonably expect an increase in the vulnerability of neurons and astrocytes to excitotoxicity and oxidative stress.

Conclusions

A considerable amount of scientific evidence demonstrates that fluoride, aluminum, and AlF_x can harm a great number of cellular functions, including mitochondrial energy production, cytoskeletal structures, plasma membrane function, glucose metabolism, critical enzymes, G proteins, neurotransmitter and endocrine receptors, immune system and inflammatory gene activation. In addition, a number of factors and sources must be considered when assessing aluminum toxicity in individual cases. Injecting aluminum adjuvants in infants and young children is particularly harmful based not only on its massive absorption, but also on their low body weight and the extreme vulnerability of the developing nervous system to toxic insults. Prolonged immunoexcitotoxicity as well as toxicity to a number of metabolic systems is of critical importance.

The discovery of synergistic action of fluoride plus Al^{3+} expanded our understanding of these mechanisms and their effects on living organism. Many investigations of the long-term administration of fluoride to laboratory animals have demonstrated that fluoride and AlF_x complexes can elicit

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impairment of homeostasis, growth, development, cognition, and behavior. It is evident that AlF_x might evoke receptor malfunction and act as a hormonal disruptor. Al^{3+} binds almost 10^3–10^7 times more strongly to ATP than does Mg^{2+} (Exley, 2014; Pogue and Lukiw, 2014), and once Al^{3+} or phosphate analog AlF_x acquire an energetically favorable electron-rich binding site, it has a tendency to remain there. In view of the ubiquity of phosphate in cell metabolism, AlF_x represent a strong potential hazard for living organisms including humans. Central nervous system disorders in humans are sensitive indicators of toxicants to which we are being exposed (Shaw et al., 2014).

Conflict of interest statement

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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REFERENCES

Bauman, M.D., Isoif, A.M., Smith, S.E., Bregere, C., Amaral, D.G., Patterson, P.H., 2014. Activation of the maternal immune system during pregnancy alters behavioral development of rhesus monkey offspring. Biol. Psychiatry 75, 332–341.

Beltrán-Aguilar, E.D., Barker, L., Dye, B.A., 2010. Prevalence and severity of dental fluorosis in the United States, 1999-2004. NCHS Data Brief 53, 1–8.

Blaylock, R.L., 2004. Excitotoxicity, a possible central mechanism in fluoride toxicity. Fluoride 37, 264–277.

Blaylock, R.L., 2012. Aluminum induced immunoexcitotoxicity in neurodevelopmental and neurodegenerative disorders. Curr. Inorg. Chem. 21, 46–53.

Blaylock, R.L., Strunecka, A., 2009. Immune-glutamatergic dysfunction as a central mechanism of autism spectrum disorders. Curr. Med. Chem. 16, 157–170.

Blaylock, R.L., Maroon, J., 2011. Immunoexcitotoxicity as a central mechanism in chronic traumatic encephalopathy – a unifying hypothesis. Surg. Neurol. Int. 2, 107.

Cadusseau, J., Ragunathan-Thangarajah, N., Surenaud, M., Hue, S., Authier, F.J., Gherardi, R.K., 2014. Selective elevation of circulating CCL2/MCP-1 levels in patients with longstanding post-vaccinal macrophagic myofasciitis and ASIA. Curr. Med. Chem. 21, 511–517.

Chuchu, N., Patel, B., Sebastan, B., Exley, C., 2013. The aluminum content of infant formula remains too high. BMC Pediatr. 13, 162–169.

Couette, M., Boisse, M.F., Maison, P., Brugieres, P., Cesaro, P., Chevalier, X., Gherardi, R.K., Bachoud-Levi, A.C., Authier, F.J., 2009. Long-term persistence of vaccine-derived aluminum hydroxide is associated with chronic cognitive dysfunction. J. Inorg. Biochem. 311, 1571–1578.

Danzer, R., Kelley, K.W., 2007. Twenty years of research on cytokine-induced sickness behavior. Brain Behav. Immun. 21, 153–160.

Du, X., Fleiss, B., Li, H., D'angelo, B., Sun, Y., Zhu, C., Hagberg, H., Levy, O., Mallard, C., Wang, X., 2011. Systemic stimulation of TLR2 impairs neonatal mouse brain development. PLoS ONE 65, e19583.

Exley, C., 2014. Why industry propaganda and political interference cannot disguise the inevitable role played by human exposure to aluminum in neurodegenerative diseases, including Alzheimer's disease. Front. Neurol. 5, 212–218.

Flarend, R.E., Hem, S.L., White, J.L., Elmore, D., Suckow, M.A., Rudy, A.C., Dandashli, E.A., 1997. *In vivo* absorption of aluminum-containing vaccine adjuvants using 26AI. Vaccine 15, 1314–1318.

Frombonne, E., 1999. The epidemiology of autism, a review. Psych. Med. 29, 769–786.

Gherardi, R.K., Coquet, M., Cherin, P., Authier, F.J., Laforêt, P., Bélec, L., Figarella-Branger, D., Mussini, J.M., Pellissier, J.F., Fardeau, M., 1998. Macrophagic myofasciitis: an emerging entity, Groupe d'Etudes et Recherche sur les maladies muscularis acquises et dysimmunitaries (GERMMAD) de l'association Francaise contre les myopathies (AFM). Lancet 352, 347–352.

Gherardi, R.K., Eidi, H., Crepeaux, G., Authier, F.J., Cadusseau, J., 2015. Biopersistence and brain translocation of aluminum adjuvants of vaccines. Front. Neurol. 6, 4–12.

Ibi, D., Nagai, T., Kitahara, Y., Mizoguchi, H., Koike, H., Shiraki, A., Takuma, K., Kamei, H., Noda, Y., Nitta, A., Nabeshima, T., Yoneda, Y., Yamada, K., 2009. Neonatal poly, C treatment in mice results in schizophrenia-like behavioral and neurochemical abnormalities in adulthood. Neurosci. Res. 64, 297–305.

Khan, Z., Combadiwre, C., Authier, F.J., Itier, V., Lux, F., Exley, Ch., Mahrouf-Yorgov, M., Decrouy, X., Moretto, P., Tillement, O., Gherardi, R.K., Cadusseau, J., 2013. Slow CCL2-dependent translocation of biopersistent particles from muscle to brain. BMC Med. 11, 99.

Luke, J., 2001. Fluoride deposition in the aged human pineal gland. Caries Res. 352, 125–128.

Mullenix, P.J., Denbesten, P.K., Kernan, W.J., 1995. Neurotoxicity of sodium fluoride in rats. Neurotoxicol. Teratol. 17, 169–177.

Parker-Athill, E.C., Tan, J., 2010. Maternal immune activation and sutism spectrum disorder, interleukin-6 signaling as a key mechanistic pathway. Neurosignals 18, 113–128.

Perry, V.H., Holmes, C., 2014. Microglial priming in neurodegenerative disease. Nat. Rev. Neurol. 10, 217–224.

Pogue, A.I., Lukiw, W.J., 2014. The mobilization of aluminum into the biosphere. Front. Neurol. 5, 262–270.

Redhead, K., Quinian, G.J., Das, R.G., Gutteridge, J.M., 1992. Aluminum-adjuvanted vaccines transiently increase aluminum levels in murine brain tissue. Pharmacol. Toxicol. 704, 278–280.

Rigolet, M., Aouizerate, J., Couette, M., Ragunathan-Thangarajah, N., Aoun-Sebaiti, M., Gherardi, R.K., Cadusseau, J., Authier, F.J., 2014. Clinical features in patients with long-lasting macrophagic myofasciitis. Front. Neurol. 5, 230–242.

Sharma, P., Mishra, K.P., 2006. Aluminum-induced material and developmental toxicity and oxidative stress in rat brain, response to combined administration of Tiron and glutathione. Reprod. Toxicol. 21, 313–321.

Shaw, C.A., Petrik, M.S., 2009. Aluminum hydroxide injections leads to motor deficits and motor neuron degeneration. J. Inorg. Biochem. 103, 1555–1562.

Shaw, C.A., Seneff, S., Kette, S.D., Tomljenovic, L., Oller Jr., J.W., Davidson, R.M., 2014. Aluminum-induced entropy in

biological systems, implications for neurological disease. J. Toxicol. 2014, 491316.

Smith, S.E., Li, J., Garbett, K., Mirnics, K., Patterson, P.H., 2007. Maternal immune activation alters fetal brain development through interleukin-6. J. Neurosci. 27, 10695–10702.

Strunecka, A., Patocka, J., 1999. Pharmacological and toxicological effects of aluminofluoride complexes. Fluoride 32, 230–242.

Strunecka, A., Strunecky, O., Patocka, J., 2002. Fluoride plus aluminum, useful tools in laboratory investigations, but messengers of false information. Physiol. Res. 51, 557–564.

Strunecka, A., Patocka, J., Blaylock, R.L., Chinoy, N.J., 2007. Fluoride interactions, from molecules to disease. Curr. Signal Trans. Ther. 2, 190–213.

Strunecka, A., Blaylock, R.L., Hyman, M., Paclt, I., 2010. In: Strunecka, A. (Ed.), Cellular and Molecular Biology of Autism Spectrum Disorders. Bentham Science Pub.

Strunecka, A., Blaylock, R.L., Patocka, J., 2012. Aluminofluoride complexes, phosphate analogs and a hidden hazards for living organisms. Curr. Inorg. Chem. 2, 8–18.

Tomljenovic, L., Shaw, C.A., 2011. Do aluminum vaccine adjuvants contribute to the rising prevalence of autism? J. Inorg. Biochem. 105, 1489–1499.

Tomljenovic, L., Shaw, C.A., 2013. Mechanisms of aluminum adjuvant toxicity and autoimmunity in pediatric populations. Lupus 21, 223–230.

Vargas, D.L., Nascimbene, C., Krishnan, C., Zimmerman, A.W., Pardo, C.A., 2005. Neuroglial activation and neuroinflammation in the brain of patients with autism. Ann. Neurol. 571, 67–81.

Varner, J.A., Jensen, K.F., Horvath, W., Isaacson, R.L., 1998. Chronic administration of aluminum-fluoride or sodium-fluoride to rats in drinking water, alterations in neuronal and cerebrovascular integrity. Brain Res. 784, 284–298.

Viezeliene, D., Beekhof, P., Gremmer, E., Rodovicius, H., Sadauskiene, I., Jansen, E., Ivanov, L., 2013. Selective induction of IL-6 by aluminum-induced oxidative stress can be prevented by selenium. J. Trace Elem. Med. Biol. 27, 226–229.

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