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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