Autism – A Potential Autoimmune Disease: Neurodegeneration-Induced Autoantibodies against Neural Proteins

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Abstract

We hypothesize that maternal neurodegeneration, resulting from a chemical, infectious or physical brain injury event, can be causative in the development of autism spectrum disorders (ASD). Following a maternal brain injury event before or during gestation, maternal neural proteins escape the breached blood brain barrier (BBB), triggering the formation of IgG autoantibodies. Subsequently, the autoantibodies cross the placenta and enter the fetal brain causing ASD. We propose the circulating maternal IgG autoantibodies (1) as a potential target for prevention, as a decrease could either possibly prevent ASD or lessen its severity, and (2) as biomarkers for screening, diagnosis and treatment of ASD in infants and children. This research on ASD has the potential to affect health care policies concerning women who are pregnant or planning to become pregnant and lead to novel treatment of ASD.

Autism Spectrum Disorder

Autism spectrum disorder (ASD) is a neurodevelopmental disorder characterized by difficulty in communication and repetitive behaviors [1]. ASD definition includes: atypical autism, high-functioning autism, and Asperger's disorder. Individuals with ASD may have extraordinarily high IQ, normal intellectual abilities, or intellectual disability (ID), known as ASD with ID. Initial diagnosis is often made as early as 18 months of age, but formal diagnosis may occur at 5-8 years [2], with boys four times more likely to be diagnosed than girls [3]. In the United States, in 2014, approximately 1 in 59 children had ASD. Approximately 70 percent of ASD diagnoses are accompanied by an additional condition such as Attention Deficit and Hyperactivity Disorder (ADHD), learning impairment, depression, or anxiety. Children with ASD may also have other disorders [1] such as: intellectual disability, epilepsy, Tourette's syndrome, difficulty sleeping, and many suffer gastrointestinal dysfunctions. Despite numerous studies on ASD there is little consensus on the mechanism, including whether the cause is genetic or environmental. Approximately 10% of ASD cases have known contributing gene mutations, while 90% are classified as idiopathic, which are thought to be caused by environmental factors.

In ASD, there is increased brain volume and an altered ratio of gray/white matter. The areas of the brain that are affected in ASD patients include the cerebellum, cortex, nuclei of the amygdala, the fusiform face. Cerebellar Purkinje cell numbers decrease while white matter neuron numbers increase [4]. The cerebellum plays an important role in fine motor control, body balance, coordination and movements and in cognition. The cerebellum in individuals with ASD has a 40–50% reduction in nicotinic cholinergic receptors such as α3, α4, and β2 [5].

Neuronal and Glial Proteins as Biomarkers for Neurodegeneration

Neuronal proteins

The brain has two billion nerve cells known as neurons and a trillion supporting cells including astrocytes and oligodendrocytes [6]. Neurons have two processes, a single axon and dendrites. Axonal protein components include neurofilament triplet proteins (NFP), tubulin,
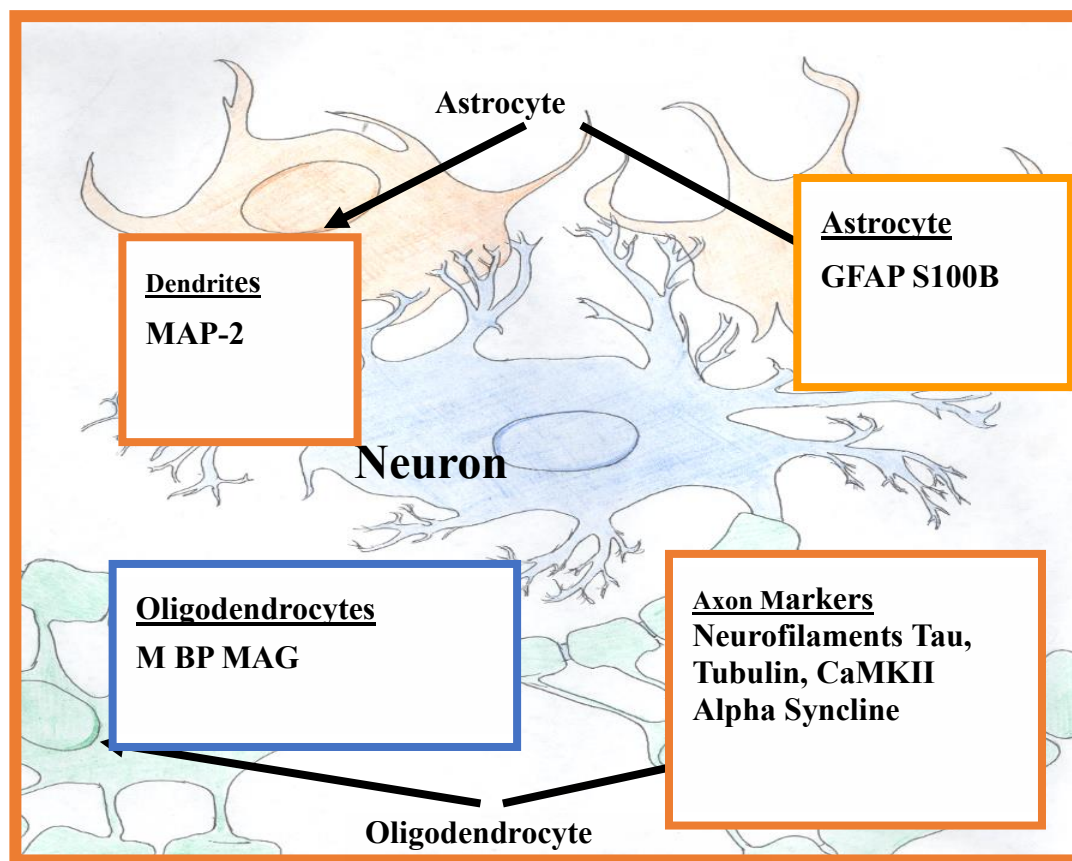
Figure 1: Schematic presentation of the neuron containing neuronal and glial biomarker proteins. 1) Axonal marker proteins consist of: Neurofilament triplet proteins: tubulin, tau, and CaMKII. 2) Oligodendrocyte proteins: MAP-2 and MAG. 3) Astrocytes proteins: GFAP and S100B.

microtubule associated protein: (tau) is present in the axon; whereas MAP-2 is confined to the dendrites. Calcium/calmodulin kinase II (CaMKII) present in the axonal cytoskeleton phosphorylates cytoskeletal proteins (Figure 1). Although tubulin is present in virtually all eukaryotic cells, it consists of approximately 10-20% of total soluble protein in the brain. Another axonal protein, alpha-synuclein has been shown to function as a neuroprotective protein, particularly with respect to oxidative stress.

Glial proteins

Myelinated axons contain myelin basic protein (MBP), myelin associated glycoprotein (MAG) and neurofascin 155 that are produced by oligodendrocytes in the brain and Schwan cells in peripheral nerves (Figure 1). In neurodegenerative disorders and diseases, there is a decrease of these proteins, resulting in the loss of insulating myelin sheath that consequently causes axonal destruction [7]. GFAP and S-100B, both of which are secreted by the astrocytes, are the only two antigens studied that are not present in the peripheral nervous system; they are consistent with brain injury. GFAP plays an important role in the long-term maintenance of brain cytoarchitecture, proper functioning of the blood brain barrier, and modulation of neuronal function. Loss of astrocytic structural integrity resulting from necrosis, or mechanical disruption causes disintegration of blood brain barrier (BBB) and the release of GFAP and S100B. S100B exerts both detrimental and neutrophic effects, depending on its concentration in brain tissue.

In brain neurodegenerative diseases, certain neural

proteins are known to pass into the cerebrospinal fluid (CSF) or leak through the blood brain barrier (BBB) into circulating blood [8]. These proteins are used as biomarkers for these diseases and conditions. For example, in traumatic brain injury (TBI), the neurofilament triplet proteins (NFP) normally found predominately in large myelinated axons [9], are elevated in cerebrospinal fluid (CSF) and serum, as is the case with microtubule-associated proteins tau which are normally present in both white matter and gray matter [10]. Aggregated Tau is used as a diagnostic marker for Alzheimer's disease [11,12]. MAP-2, the most abundant microtubule-associated protein in the mammalian brain, is found in the dendrite [13] and is a biomarker for Purkinje cell damage; it is also a sensitive biomarker for brain lesions related to seizures [14]. Tubulin, another known neurodegenerative biomarker present in almost all eukaryotic cells comprises approximately 10-20% soluble proteins in the brain [13]. Calcium/calmodulin kinase II (CaMKII) that accounts for 12% of all proteins in the brain phosphorylates cytoskeletal proteins such bas MAP-2, tau, tubulin and NFP are known neurodegenerative biomarkers [15]. Myelinated axons contain myelin basic protein (MBP) and myelin associated glycoprotein (MAG). MBP is elevated in multiple sclerosis and stroke [16]. α-synuclein acts as a neuroprotective protein against oxidative stress [17]. The astrocytic protein glial fibrillary acidic protein (GFAP) contributes to white matter architecture, myelination, and integrity of the blood-brain barrier. The S100B, an astrocytic protein, stabilizes proteins associated with microtubules, such as tau and MAP-2. An increase in S100B, in micromolar concentrations, has been observed in TBI and toxic or ischemic brain damage, and has been used as a prognostic marker. At nano concentration, S100B acts as a neurotrophic factor and is used as a biomarker for major depression [18]. Furthermore, Immunoreactivity of S100B is increased in Down's Syndrome and Alzheimer's disease [19]. It is important to realize that the use of blood circulated neural proteins as biomarkers for neurodegenerative diseases is limited because of their instability to proteases in blood. For example, the half-life of GFAP in serum is less than 2 days [20] and that of S100B is 2 hours [21].

Hypothesis: Neurodegeneration-Induced Autoimmunity and Autism

We hypothesize that infections, or exposures to chemicals such as air pollutants, heavy metals and pesticides. physical injury of the brain, radiation, shortly before or during pregnancy, can indirectly lead to autism by causing neurodegeneration and release of proteins across impaired BBB and subsequent formation of autoantibodies to neural proteins. Normally B lymphocytes produce antibodies, to proteins, whereas T

cells are responsible for cell-mediated immune responses [22]. During pregnancy, maternal IgG antibodies protect the unborn child by crossing the placenta and the fetal BBB during development and persisting in the newborn for up to 6 months postnatal [23]; at 30 weeks it reaches 50% of circulating levels in the mother [24] and exceeds that of the mother, at birth.

Following neuronal cell death, neuronal proteins leak from the damaged neurons and glial cells into circulation, and through the breached BBB. Once in the bloodstream, these proteins act as antigens and activate B lymphocytes to form autoantibodies. Pathogenic autoantibodies (IgG) are produced when the balance between B-cell activation and inhibitory signals is disturbed [25]. IgG autoantibodies cross the placenta and fetal BBB and disrupt the neural development by binding to key neurons in the cerebellum and altering their functions [26]. This neurodevelopmental disruption in the developing fetus leads to ASD [27]. Immunologic risk factors include genetics and family history of autoimmune disease [28]. Our hypothesis is supported and is consistent with the results of many published reports that are summarized below.

Our hypothesis is in agreement with the reports of Croen et al. [29,30] showing presence of mid-pregnancy autoantibodies to fetal brain proteins and their use as early markers for ASD. Similarly, autoantibodies to cerebellum correlate with behavior in ASD children [31]. Several investigators have reported certain autoantibodies in children with ASD and their non-autistic siblings which have been shown to be against unidentified brain proteins [31-39]. The masses of the unknown proteins correspond to particular neuronal and glial proteins [40].

The results of our recent preliminary study showing significant elevation of the autoantibodies against neuronal and glial proteins in the serum of children with ASD and their mothers, compared to age-matched normal control children and their mothers is consistent with our hypothesis [40]. The results revealed a substantial increase of autoantibodies in ASD children and, to a lesser extent, in their mothers, compared to healthy controls in the following ascending order: MAP-2 > NFP > MBP > MAG > α-syncline> S100B and GFAP, CamKII, whereas tubulin and tau were not statistically different from controls. These results support the postulation that ASD is an autoimmune disease [41].

Earlier findings that ASD can be triggered by the mother's exposure to environmental agents or toxicants shortly before or after conception is in agreement with our hypothesis. The finding that the first or second trimester is the period of neural vulnerability to environmental

exposure leading to ASD [28,42] is consistent with our hypothesis. These exposures include maternal infections associated with fever [43], immune activation [44], significant bleeding during the second trimester [45] or occurrences of cytomegalovirus infection during the third trimesters [46] which cause neural degeneration.

Our hypothesis is also consistent with reports of increased development of ASD following exposure to insecticides. Although insecticides were developed to interfere with nervous system functions by causing disruption of neurotransmitters such as GABA by chlorinated hydrocarbons or acetylcholine signaling by organophosphorus compounds leading to animal death [15], recent studies showed that these chemicals also cause neuronal cell death [47,48]. Furthermore, commonly used insecticides are lipid-soluble and are able to pass through the BBB and placenta through endogenous transporters. A case-control study conducted in California found some indication of elevated risk for development of ASD exposure to *p,p*-DDE [49]. A recent epidemiological study showed that mothers exposed to pesticides near conception increased their likelihood of having children with ASD [50]. The associations between ASD diagnoses or symptoms and exposure to organochlorine, organophosphate, and pyrethroid pesticide during pregnancy has also been reported [51-54]. The finding of Abdel-Rahman et al. [55] of the formation of autoantibodies against neuronal and glial proteins in patients exposed to pesticides who developed neurological symptoms characteristic of those caused by organophosphate insecticides adds more support to our hypothesis.

In agreement with our hypothesis is the development of ASD following parental exposure to environmental toxicants such as diesel, lead, manganese, mercury, methylene chloride, mercury, cadmium, nickel, trichloroethylene, and vinyl chloride [56,57], volatile organic compounds [58], and plasticizers [59-61]. Many of these chemicals have been shown to cause neural cell death [6]. Similarly, the finding that *in-utero* exposures to valproate that causes cell death [62] and other anticonvulsants also appear to increase the risk for developing autism [63]. Further examples are sychotropic medications [64,65], thalidomide [66], as well as misoprostol in northern Brazil [67].

Neuroprotection from ASD by maternal intake of folic lends a strong support to support our assertion that neural cell death leads to the formation of autoantibodies and subsequent development of ASD. Studies have shown a folic acid-induced neuroprotective mechanism that may be due to anti-apoptotic properties of the folic acid [68]. Studies have also shown that maternal intake of folic acid resulted in diminished risk for ASD in genetically susceptible mothers [69]. It is in agreement with studies showing altered immune function such as autoimmune disorders or cytokine changes in individuals with ASD as well as their mothers [70] that contribute to ASD development [71].

Our hypothesis agrees with opinion that ASD is a neuroimmune and neurodegenerative disorder [72] that involves breakdown of the BBB [73]. It is also in agreement with the reports that in some cases, children with ASD exhibited evidence of activated microglia and astrocytes, elevated 8-oxo-guanosine levels, evidence of oxidative stress, the presence of pro-inflammatory cytokines, and neuronal cell loss [74]. This contrasts with the position of the World Health Organization that considers ASD to be a developmental disorder exclusively affected by environmental factors and genetics, rather than predominately the effect of neurodegeneration [74]. Finally, the presence of autoantibodies in ASD is similar to detection of autoantibodies in plasma from patients with Touretts's syndrome that was reported to be present in some ASD children [75].

If this hypothesis is confirmed in large studies, ASD may be treated using therapies that render normal B cell function and eliminate pathogenic autoantibodies by selectively depleting antibody producing B cells [76]. A possible treatment is rituximab (rituxan) that is used to reduce B cells, without causing toxicity. Rituximab, a monoclonal antibody against the cell surface receptor, CD20 present in B cells [77]. Several autoimmune diseases have been treated with rituximab including rheumatoid arthritis, granulomatosis with polyangiitis, and other antineutrophil cytoplasmic antibody-associated vasculitis [77,78]. Further, the use of rituximab in treatment of patients with chronic fatigue syndrome has led to a suggestion that chronic fatigue syndrome may have an autoimmune component [79].

Declaration of Interests

The author reports no conflict of interest. The author is solely responsible for the content and writing of the article.

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