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Autoimmunity in Autism Spectrum Disorders

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1. Introduction

Autism spectrum disorders (ASD) are part of a broad spectrum of neurodevelopmental heterogeneous disorders known as pervasive developmental disorders (PDD), which include autism, Asperger's syndrome, Rett's disorder, and childhood disintegrative disintegrative disorder. By description, ASD are characterized by impairments in verbal and nonverbal communication and social interaction (Association, A. P., 1994), with onset usually around the first 36 months of childhood. Repetitive, stereotyped, purposeless behaviors as well as attention and sensory dysfunctions are common findings in patients with ASD. Over the last few years, the prevalence of ASD has increased dramatically, and this increase, cannot be attributed entirely to improved diagnostic techniques and increased awareness only (Fombonne, 2003). Latest reports estimate that ASD affects approximately one per one hundred persons, with a male-to-female ratio of four to one (4:1) (Fombonne, 2003). Despite that the fact there is increase in ASD research worldwide, the exact etiology of autism and ASD remains largely unknown. Over the last few years, a scientific interest has occurred in the close relationship of the immune system to the central nervous system leading to considerable expansion in the field of psychoneuroimmunology. And currently it is widely accepted that environmental factors can compromise the immune system. A multi directional scientific approach has been adopted by many scientists in their research journey as it is likely to result from a complex combination of environmental, neurological, immunological, and genetic factors. There is emerging evidence and growing concern that a dysregulated or abnormal immune responses play an important role in some forms of ASD. In general, the associations between the immune and neurological systems are becoming more evident in many neurological disorders. Behaviors such as mood and sleep can be altered by cytokines and other products of immune activation, due to widespread effects on neurons. Aberrant immune activity during the early critical periods of brain and neuronal development could potentially play a role in neuronal dysfunction. Several efforts have attempted to link dysfunctional immune activity and ASD, such as maternal immune abnormalities during early pregnancy, increased incidence of familial autoimmunity, and childhood vaccinations. Several lines of research have shown abnormalities of the immune response in autism, including abnormal generation of antibodies, cytokines, and immune cells. The following chapter is a review of current research linking immune dysfunction to ASD.

2. Neurological abnormalities in autism spectrum disorders

Neural development takes place during the early years of life. During this period of time, neuronal differentiation, migration, axonal extension, and synapse formation takes place in an accurately designed sequence of events. In ASD, many neurological abnormalities have been found, which suggest that normal neurodevelopment was disturbed during a critical time of development, which include proliferation, migration, differentiation, synaptogenesis, gliogenesis, myelination, and apoptosis of neurons (Rice & Barone Jr., 2000). This critical time period extend from embryonic stage up until adolescence, with period of overlap at some stages. Quarter of autistic patients undergo a period of autistic regression, around 18th–24th months of age, during which they experience loss of previously acquired language and behavioral skills (Fombonne, 2003). Postmortem and neuroimaging magnetic resonance imaging (MRI) studies played an important role in the discovery of many neurological abnormalities in autistic patient's brains. These studies have suggested that many major brain structures may be affected in autism, including cerebellum, cerebral cortex, amygdala, hippocampus, corpus collosum, basal ganglia, and brain stem (Akshoomoff et al.,2002; Acosta et al., 2004; Courchesne et al., 2001). These abnormalities suggest multiple periods of prenatal onset. Furthermore, brain regions implicated in ASD tend to develop more slowly and are more vulnerable to disturbances. Cerebellar abnormalities have been observed as the most consistent finding in ASD, targeting in particular Purkinje and granular cells (Courchesne, 2002). Another important area which was found to be abnormal in ASD is the limbic system. The limbic system, whose components include the amygdala, hippocampus, cingulate gyrus, and septal nuclei, consists of a group of nuclei unified by a common function. The limbic system controls emotional behavior and any changes in body state that accompany this behavior, such as heart rate blood pressure, and respiration rate. Due to its role in emotion, the limbic system is of major interest in ASD patients; so far, the abnormal findings include increased cell packing and small neuronal size, indicative of cellular, maturational arrest (Akshoomoff et al., 2002; Palmen et al., 2004). Other neurological abnormalities described in ASD are abnormal EEG findings: around third of children with ASD develop epilepsy by adolescence (Volkmar et al., 1999), and an additional, significant minority has subclinical epilepsy, as measured by epileptiform encephalogram, especially during sleep (Tuchman et al., 1991). These findings clearly indicate that there are neurological involvements in ASD that affect the development and differentiation of neurons in the brain.

2.1 Structural magnetic resonance imaging findings

Structural magnetic resonance imaging (SMRI) studies played a major role in highlighting brain changes in ASD. SMRI confirmed the increase in total brain volume in autism, which present as increase in head circumference, starting around 2 to 4 years of age (Hazlett et al., 2005, Courchesne et al., 2001). This increase was attributed mainly to increase in total cerebral white matter and total cortical gray matter. The inner zone of white matter, especially the corpus callosum and internal capsule, showed no volume increase. The volume of the outer radiate white matter was increased in all cerebral lobes but with a frontal predominance. Collectively, these findings were interpreted as evidence of overgrowth of short- and medium-range intrahemispheric corticocortical connections with no detectable involvement of interhemispheric connections or connections between cortex and subcortical structures. The onset of brain overgrowth coincided with the onset of the

signs and symptoms of autism, signifying that the overgrowth was part of a pathologic process that disrupted the development of normal brain structure and function in autism. A recent study, by Jieun et. al., (2010), recruiting a narrow age range of children with ASD and age-matched typically developing (TD) children, evaluating alterations in subregional amygdalar morphology. The group showed a bilateral enlargement of laterobasal subregions of the amygdala in 6- to 7-year-old children with ASD and that subregional alterations are associated with deficits in social and communicative behavior (Jieun et al., 2010)

2.2 Functional magnetic resonance imaging studies findings

Further understanding of autism was made from functional magnetic resonance imaging (fMRI) studies. During cognitive processing, subjects with autism use the same cortical areas, compared to aged matched control. Important remarkable variations have been found in the patterns of activation and in the timing or synchronization of the activation across the cortical network recruited to perform different tasks. fMRI study of written sentence comprehension has indicated that high-functioning adults with autism has relatively higher levels of activation in the left posterior superior temporal gyrus (Wernicke) and relatively lower levels of activation in the left frontal inferior gyrus (Broca) compared with age- and IQ-matched controls (Just et al., 2004). In addition, a reduction in functional connectivity, that is the correlation of the time series of the activation among cortical regions participating in performance of higher order tasks, was noted. Lower functional connectivity relative to the control group among participating cortical regions has been found in fMRI studies involving language (Just et al., 2004; Kana et al., 2006) working memory (Koshino et al., 2005), problem solving (Cherkassky et al., 2007), and social cognition (Castelli et al., 2002) providing further evidence of a general problem with functional under connectivity, within and between neocortical systems in autism. Functional imaging findings in autism have been consistent with a cognitive style favoring the use of visuospatial coding strategies, evident in increased reliance on extra striate and parietal regions (Manjaly et al., 2007). This could reflect a disruption in fronto-striatal and fronto-parietal functional connectivity (Just et al., 2007), abnormal activation within frontal and temporal regions has been related to the linguistic difficulties in this population (Groen et al., 2008).

2.3 Cortical connectivity in autism spectrum disorders

Cortical connectivity was examined in autism spectrum disorders by comparing gyral and sulcal thickness as indices of short- and longer-distance cortical connections (Hardan et al., 2006). The results showed an overall increase in cortical thickness in 8 to 12year old boys with autism compared to control. Furthermore, the study demonstrated that cortical thickness in sulci (long connections) was greater (analogous to increased volume of outer radiate white matter) than in gyri (short vertical connections), which is comparable to the findings of Herbert and colleagues for white matter (Herbert et al., 2004). Another significant finding was abnormalities in minicolumns structure in brain of autistic children. Minicolumns are composed of radically oriented arrays of pyramidal neurons (layers II-VI), interneuron's (layers I-VI), axons, and dendrites. Minicolumns assemble into macrocolumns, which form receptive fields. Minicolumns have been hypothesized to be the smallest radial unit of information processing in the cortex, but this function has not been confirmed. In autism spectrum disorders, reports indicate an increase in miniclomns number but narrower in width, with reduced neuronal space, with smaller neuron cell bodies and nucleoli

(Casanova et al., 2006). These abnormalities have been observed bilaterally in cortical areas 3, 4, 9, 17, 21, and 22. The description of these cortical abnormalities provides a critical counterbalance to the numerous reports of increased white matter volume, which might otherwise have led to a white matter model of autism. Findings of atypical patterns in both functional and anatomical connectivity in autism have established that autism is a not a localized neurological disorder, but affects many parts of the brain in many types of cognitive tasks. fMRI studies repeatedly find evidence of decreased coordination between frontal and posterior brain regions in autism, as measured by functional connectivity. In addition, neuroimaging studies have also revealed evidence of an atypical pattern of frontal white matter development in autism. These findings indicate that limitations of brain connectivity give rise to the varied behavioral deficits found in autism. As research continues to investigate these biological mechanisms, new intervention methods may develop to help improve brain connectivity and overcome the behavioral impairments of autism.

3. Autoimmunity in autism spectrum disorders

3.1 General immunological findings in autism spectrum disorders

Autoimmunity develops when the immune system is inappropriately directed to recognize and exert an exaggerated response to self components. The exact mechanism of autoimmunity in autoimmune diseases is not identical, but they all have autoreactive antibodies and T cells. The presence of antibodies directed against components of the CNS in the sera of autistic children is indicative of an autoimmune process that may be involved in the pathology of some cases of ASD. Almost with all autoimmune diseases, genetic, immune and environmental factors, such as, diet, toxic chemicals and infections, play critical roles in the development of the disease (Buehler, 2011; Vojdani et al., 2002; Kiberstis et al., 2002). Casein, casomorphins, gluten (GLU) and gluteomorphins, the opioid peptides, which is present in a range of food sources, are all implicated in the etiology of autism spectrum disorders. These peptides can stimulate T-cells, induce peptide specific T cell responses, and can lead to abnormal levels of cytokine production, which may result in inflammation, autoimmune reactions and disruption of neuroimmune communications (Jyonouchi et al., 2001). In autism spectrum disorders majority of children have wheat and milk protein intolerance. And accordingly, removal of these peptides from the diets significantly improves their conditions (Vojdani et al., 2002). Immunoglobulines, such as, IgG, IgM and IgA, were detected, against nine specific neuron-specific antigens in the sera of children with autism (Vojdani et al., 2002). These antibodies were found to bind with different central nervous system molecules that have sequence homologies to a milk protein.

Long exposure to toxic, environmental or occupational chemicals, have been shown to stimulate the production of autoantibodies to nervous system antigens. Titers of antibodies against neurofilaments and myelin basic protein (MBP) correlated significantly with urinary mercury and blood lead levels, the standard indicators of toxic exposure. In addition, levels of these antibodies proved to correlate with sensorimotor deficits. Gut-associated lymphoid tissues (GALT) can interact with toxins, chemicals and pollutants. If covalent reactions are formed between the drugs or other chemical compounds and the GALT, this can lead to immune responses and chemically-induced Type I- Type IV allergic reactions (Salama et al., 1989). Many infectious agents including measles, Rubella virus and Cytomegalovirus vaccines have long been suggested as etiologic factors in autism (Chess et al., 1978.; Wakefield et al., 1998; Ivarsson et al., 1990).

A complex communication system does exist between the nervous and the immune system, during normal and pathological conditions. Alteration in brain function can result from immune cells and molecules, such as cytokines and chemokines. This might affect cognition and emotions. Furthermore, immune cells and immune molecules can result in neuronal modulation of systemic CNS responses to infection, injury, and inflammation. The cytokines have been shown to directly affect neural tissue function and development, especially the proinflammatory cytokines such as interleukin (IL)-1, IL-6, IL-12, interferon-(IFN), and tumor necrosis factor (TNF) (Jarskog et al., 1997; AL-Ayadhi, 2005a). Inflammatory cytokine IL-6 can induce sleep, and TNF can provoke anorexia (Steinman et al., 2003; Tracey et al., 1988). Cytokines have been suggested to be responsible for many common features of autism, such as mood and sleep disturbances. In turn, neuropeptides, derived from the central and peripheral nervous system, have profound effects on the immune system, including the chemotaxis and recruitment of innate immune cells (Tracey et al., 1988). A dysregulated immune function has been suggested by many scientists. Systemic, immunologic abnormalities in autism have been related to autoimmunity, leading to the generation of antibodies that are reactive to CNS proteins and have the potential for neuronal tissue destruction, or leading to an inappropriate or ineffective immune response to pathogen assault (Korvatska et al., 2002). Several immune abnormalities, suggestive of, dysregulated immune response reported in autistic children include incomplete or partial T cell activation evidenced by increased numbers of T cells without the expression of the -2 receptor (IL-2R) (Warren et al., 1986; Plioplys et al., 1994), dysregulated apoptosis mechanisms (Korvatska et al., 2002), decreased peripheral lymphocyte numbers [30], decreased response to T cell mitogens (Warren et al., 1986; Stubbs et al., 1977) and the imbalance of serum Ig levels [30, 57]. Furthermore, immune-based genes including class II HLA-DRB1 alleles, class III complement C4 alleles, and HLA-extended haplotypes have been linked to autism spectrum disorders (Odell et al., 2005; Torres et al., 2001).

Animal models have also contributed to strengthening the dysregulated immune system hypothesis in the etiology of autism spectrum disorders which indicate that the maternal immune response to infection can influence fetal brain development via increased levels of circulating cytokines (Yamashita et al., 2003; Patterson et al., 2002). Mouse models of maternal influenza virus infection at mid-gestation have similar neuropathological and behavioral abnormalities in the offspring, which are consistent with those seen in autism and were again suggestive of a strong immune component (Patterson, 2002; Shi et al., 2003). Furthermore, infection of neonatal rats with Borna disease virus (BDV) leads to neuronal death in the hippocampus, cerebellum, and neocortex and a behavioral syndrome that has similarities to autism (Hornig, 2002). These abnormalities are correlated with major alterations of cytokine expression in various brain regions, indicating a likely role of cytokines as mediators of CNS injury in this model (Buehler, 2011; Plata-Salaman et al., 1999; Sauder & de la Torre, 1999).

Autoimmunity was first linked to autism in a study of an autistic child, with strong family history of autoimmune diseases (Money et al., 1971). This study suggested that an inherited risk of autoimmunity could increase the risk of developing autism. Another study, investigated the frequency of autoimmune disorders in family members of 61 ASD children and 46 typically developing normal controls, and showed the mean number of autoimmune disorders to be greater in families with autism (Comi et al., 1999). In most of these cases, the individual with the autoimmune disorder was a first-degree relative (i.e., a sibling or a parent) of the autism child (Comi et al., 1999). A variety of anti-brain antibodies have been found in

autistic patients, including autoantibodies to serotonin receptor , myelin basic protein (MBP), neuron axon filament protein, cerebellar neurofilaments, nerve growth factor, 2-adrenergic, adrenergicbinding sites, anti-brain endothelial cell proteins, and antibodies directed against an as-yet unknown brain protein (Rosse et al., 2011; Buehler, 2011; AL-Ayadhi, 2005b; Singh et al., 1993; Singh et al., 1997; Todd et al., 1988; Connolly et al., 1999; Silva et al., 2004; Todd & Ciaranello, 1985). However it is still unclear as to the pathophysiological significance of these antibodies reported in children with ASD. For instance, increased autoantibodies is suggestive of increased neuronal damage, as is the case in multiple sclerosis, and other autoimmune diseases, where following demyelination, MBP is unmasked, and there is a subsequent generation of antibodies. Nevertheless, evidence of demyelination in autism has remained indefinable (Rumsey & Ernst, 2000). In one study, Glial fibrillary acidic protein (GFAP) measured in the CSF of 47 ASD children, was significantly elevated compared with 10 age-matched control children, suggesting that gliosis and unspecific brain damage may occur in autism (Ahlsen, et al., 1993). However, as GFAP correlates strongly with age, this is likely to be the result of age-dependent expansion of fibrillary astrocytes, and hence the data needs to be interpreted cautiously (Delneste, et al., 1999). Nevertheless, the importance of the presence of serum antibodies to brain tissues, regardless of the absence of neuronal damage is to be acknowledged. Singh and Rivas (2004), demonstrated antibodies directed to the rat caudate nucleus (the portion of the brain responsible for assembly of peripheral information) in 49% of the autism patients evaluated, but in none of the control cases. The observations of elevated anti-CNS antibodies in autism are at best unconfirmed and in some cases, such as serotonin receptors and MBP, are contradictory. It is important to keep in mind the difficulty in determining whether the autoantibodies present in the plasma of patients with autism contribute to the development of the disorder or if they are a consequence of the disease. Also, findings of autoimmunity in families of children with ASD suggest that in some patients, autoantibodies that target the CNS may be a pathological or an exacerbating factor in the neuronal development of children with ASD. However, increased autoimmunity may be limited to a subset of autistic patients (Buehler, 2011; Singh & Rivas, 2004). An important finding was reached by Wills research group (2009), they demonstrated that 21% the positive autoantibodies samples, reacted intensely with GABAergic Golgi neurons of the cerebellum while no samples from non-sibling, typically developing children showed similar staining (Wills et al., 2009). Further more, Rossi et al., (2011), demonstrated that 42% of controls and subjects with ASD were positively immunoreactive to some neural element, such as, cerebellar Golgi, interneurons, molecular layer of the dentate gyrus, and neuronal nuclei. Interestingly, children whose plasma reacted to brain tissue had scores on the Child Behavior Checklist (CBCL) that indicated increased behavioral and emotional problems. Children whose plasma was immunoreactive with neuronal cell bodies scored higher on multiple CBCL scales (Rossi et. a., 2011).

It is quite interesting to mention the results of a large cohort study consisted of all of the children born in Denmark from 1993 through 2004 (689 196 children). The study concluded the following: associations between family history of type 1 diabetes, infantile autism and maternal history of rheumatoid arthritis and ASDs were confirmed from previous studies. A significant association between maternal history of celiac disease and ASDs was observed for the first time. The observed associations between familial autoimmunity and ASDs/infantile autism are probably attributable to a combination of a common genetic background and a possible prenatal antibody exposure or alteration in fetal environment during pregnancy (Nancy et al., 2011).

3.2 Maternal immune system status findings

Maternal immune abnormalities such as autoimmune diseases, asthma, and allergies during pregnancy were investigated for a link to autism by Croen and colleagues (Croen, et al., 2005). They found no strong evidence linking maternal autoimmune diseases and autism. However, it was found that mothers diagnosed with asthma or allergies during their second trimester were more than twice as likely to have a child with autism (Croen, et al., 2005). To date, no studies have demonstrated that ASD children have an increased frequency of other autoimmune disease, the exception being whether ASD itself could be considered an autoimmune disease. Furthermore, due to the fact that the manifestation of autoimmune disease occur around the age of 30 and upward, and as the ASD cases studied are pediatric cases, it is worth following up the ASD cases to determine whether more autoimmune diseases will be observed as they mature. Serum from a mother with an autistic child was found to bind to Purkinje cells and other neurons, when injected into gestating mice. Furthermore, a behavioral change in mice was observed in the offspring, including altered exploration, motor coordination, and changes in cerebrallar magnetic resonance spectroscopy. On the other hand, mice injected with sera from mothers with typically developing children showed no behavioral changes (Dalton et al., 2003). This study supports the suggestion that maternal antibodies may influence neurodevelopmental processes in a subset of autism cases.

Interlukin 1 (IL-1) plays a key role in mediating severe placental damage and neurodevelopmental anomalies in offspring, as revealed by Girard et al. (2010). This group demonstrated that at the end of gestation, exposure of pregnant rats to systemic microbial product (LPS) triggers placental inflammation and massive cell death, fetal mortality, and both forebrain white matter and motor behavioral alterations in the offspring. All these effects are alleviated by the coadministration of IL-1 receptor antagonist, suggesting a possible protective treatment against human placental and fetal brain damage (Gerard et al., 2010)

3.3 Cytokines role in autism spectrum disorders

Cytokines (Chemokines) are a family of small proteins secreted by immune cells. They have the ability to induce directed chemotaxis in nearby responsive cells. Some chemokines are considered pro-inflammatory and can be induced during an immune response to recruit cells of the immune system to a site of infection. These proteins exert their biological effects by interacting with G protein-linked transmembrane receptors called chemokine receptors found on the surfaces of their target cell. Several studies have demonstrated elevated plasma levels of IL-12 and IFN- in autistic children compared with controls, with no changes for IL-6, TNF- and IFN- (Singh, 1996) plasma levels, suggesting a potential TH1 shift. On the other hand, another study demonstrated, higher plasma IFN- in 10 autistic children compared with adult control subjects (Jyonouchi et al., 2005). Moreover, an increased plasma IFN- levels were observed in 29 autistic children; with a positive correlation with the generation of the intercellular CNS messenger and marker of oxidative stress, nitric oxide (NO) (Sweeten et al., 2004). The same research group observed that the macrophage product neopterin, was higher in serum samples from individuals with ASD compared with controls, which may reflect increased cell-mediated immune activation and IFN- production (Sweeten et al., 2003). Higher IFN- and neopterin levels correlated significantly with elevated, circulating numbers of monocytes observed in autistic children (Sweeten et al., 2003) with elevated urine levels of neopterin and biopterin (Messahel et al., 1998).

In cell culture experiments, in which intracellular cytokine production was examined in 20 autistic patients, compared with 20 aged-matched controls, intracellular production of IL-4 was increased, with a reduction in IFN- and IL-2 in CD4 and CD8 lymphocytes following stimulation (Gupta et al., 1998), suggestive of a TH2 bias. In vitro studies of peripheral blood mononuclear cells stimulated with lipopolysaccharide (LPS), showed an inappropriate innate immune response evidenced by amplified production of proinflammatory cytokines TNF- and IL-1 in ASD patients compared with controls (Jyonouchi et al., 2001). This immune dysregulation of increased TNF- was also found in primary sibling family members of patients with ASD, indicating a possible similar genetic susceptibility in the patients studied. This emphasizes the importance of carefully controlled, age-matched studies in the field of ASD. Moreover, the diversity of the findings reinforces the idea that ASD consists of many different phenotypes, which share the same behavioral commonalities. Cytokines can activate and exert trophic effects on glial cells, which can in turn produce cytokines and chemokines upon such activation. Cell culture studies have shown that neuropoietic cytokines such as IL-6 can have direct effects on neurons and glia, including changes in proliferation, survival, death, neurite outgrowth, and gene expression (Gadient. & Patterson, 1999; Mehler & Kessler, 1998). As the CNS is populated largely by astroglia and microglial cells, these cytokine-cell interactions are important for neuronal cell functioning and development. Immune activation in postmortem brain specimens and CSF from subjects with autism have found neuroinflammation in the cerebral cortex and cerebellum of brain tissue in autism was found. This inflammatory process was characterized by a marked cellular activation of microglial and astroglial cells and the presence of an altered cytokine pattern. In addition, there was an accumulation of perivascular macrophages and monocytes but an absence of lymphocytes and antibody from the brain specimens, suggestive of an innate immune activation. In addition, an enhanced proinflammatory cytokine profile was observed in their CSF. Abnormal immune responses in the neuroglia of autistic patients was suggested, which in turn may influence neural function and neural development, and an aberrant immune response may contribute to the development of autism. In general, the brain and CNS are considered to be protected and isolated from potentially harmful pathogens or agents within the blood, including inflammatory immune cells and proteins, by the blood brain barrier (BBB). Cytokines however, can gain entry into the brain through active transport mechanisms or at circumventricular regions, where the barrier is less controlling (Wilson et al., 2002). Impairment of the BBB function may happen as a result of binding of cytokines and inflammatory mediators to receptors on the endothelial cells directly. In addition, cytokines can migrate into the brain from the blood via the CSF to the choroid plexus or from the blood to either the subarachnoid space or parenchymalperivascular space, resulting in alteration in immune responses and production of cytokines (Ransohoff et al., 2003).

Peripheral cytokines can directly affect afferent neurons and their functions (Dantzer et al., 1998). Immune organs such as bone marrow, thymus, spleen, and lymph nodes play an important role in immune system development. Additionally, immune response is capable of changing expression and distribution of neural receptors in these organs (Mignini et al., 2003). Thus the relationship is reciprocal between immune system and neural receptors. Cytokines can affect many behaviors such as, sleep, mood, appetite and nutritional uptake, exploratory behavior, and, social interactions and communication. Systemic cytokine administration at therapeutic doses of IFN-, IL-2, and TNF can result in mood changes, sleep

disorder, decreased exploratory behavior, impaired cognitive function, and changes in enthusiasm and motivation (Larson , 2002; Licinio et al., 1998). Systemic administration of cytokines can produce an increased noradrenergic, dopaminergic, and serotonergic metabolism in the hypothalamus, hippocampus, and nucleus accumbens and modulate synaptic plasticity and thereby alter memory and learning (Zhao, B., & Schwartz, J. P., 1998). Many studies have demonstrated abnormal levels of blood lymphocytes in autism. Significantly decreased CD4 T cells have been observed in ASD (Warren et al., 1990; Denney et al., 1996; Ferrante et al., 2003; Yonk et al., 1990). In animal models, systemic T cell deficiency in mice have been shown to result in learning and memory impairment, which is reversible by T cell replacement (Kipnis et al., 2004). Furthermore, an incomplete or partial activation of T cells following stimulation, with an increased expression of HLA-DR but not the IL 2R chain (CD25), was observed in ASD (Engstrom et al., 2003; Plioplys et al., 1994).

NK cells are an important cytotoxic cell subset of the innate immune system and a major producer of cytokine. Reduced levels of circulating numbers of NK cells number and activity was observed in children with ASD and other related neurodevelopmental disorders, such as, Rett syndrome, compared with controls (Fiumara et al., 1999; Warren et al., 1987). In turn this reflects on its ability to eradicate or prevent viral infections in these children, which could potentially be damaging to neural tissues during critical windows of CNS development. Abnormal concentrations of plasma Ig classes have been observed in some ASD children with increased IgG2, IgG4, IgM and IgG (Ashwood et al., 2003; Croonenberghs et al., 2002; Trajkovski et al., 2004), highly indicative of an underlying autoimmune disorder and/or an atypical susceptibility to infections.

Cytokines activity in the brain tissue of ASD and matching normal subject was examined by Xiaohong et al., (2009). Results showed that proinflammatory cytokines (TNF- α, IL-6 and GM-CSF), Th1 cytokine (IFN-γ) and chemokine (IL-8) were significantly increased in the brains of ASD patients compared with the controls. However the Th2 cytokines (IL-4, IL-5 and IL-10) showed no significant difference. The Th1/Th2 ratio was also significantly increased in ASD patients. They concluded that ASD patients displayed an increased innate and adaptive immune response through the Th1 pathway, suggestive of a localized brain inflammation and autoimmune disorder involvement in the pathogenesis of ASD (Xiaohong et al., 2009). Flow cytometric analysis of NK cells demonstrated increased production of perforin, granzyme B, and interferon gamma (IFNγ) under resting conditions in children with ASD. Following NK cell stimulation in the presence of K562 target cells (cells used to assess NK cell cytotoxicity), the cytotoxicity of NK cells was significantly reduced in ASD compared with controls. Furthermore, under similar stimulation conditions the presence of perforin, granzyme B, and IFNγ in NK cells from ASD children was significantly lower compared with controls. Suggestive of possible dysfunction of NK cells, predisposing to the development of autoimmunity and/or adverse neuroimmune interactions during critical periods of development (Enstrom et al., 2009).

3.4 Neurokines role in autism spectrum disorders

Neurokines (neuropoietic cytokines), are neuronal related cytokines, that regulate cell numbers in the nervous system and influence functional activities of neurons. They are important mediators within the neuroimmune network. These factors are not produced exclusively by brain cells and their activities are not restricted to neurons only. Factors with neuropoietic activity include CNTF (ciliary neuronotrophic factor), CDF (cholinergic

differentiation factor, LIF (leukemia inhibitory factor), Oncostatin M but also IL6, (BDNF, NGF, NT-3, NT-4, NT-4, NT-6, GDNF) and factors produced in, or acting upon, the nervous system such as bFGF, Interleukins, or TGF-beta.

There is continual communication between the immune and nervous systems with many peptides playing a role in both. It has been proposed frequently that abnormalities in the levels and actions of neurotransmitters or neuroactive compounds during early critical windows of neurodevelopment may lead to the onset of autism. Neurotransmitters and neuropeptides not only have important key roles in the development and organization of neural tissue but also influence almost all body functions including the immune system. Numerous transmitter systems, including acetylcholine, serotonin (5-HT), dopamine, epinephrine, norepinephrine, oxytocin, vasopressin, glutamate, and _-aminobutryic acid (GABA), have been studied in ASD (Lam et al., 2006). For example, in postmortem brain specimens obtained from patients with ASD, there was a 48– 61% decrease in glutamic acid decarboxylase, an enzyme that converts glutamate into GABA, in the parietal and cerebellar regions of the brain compared with controls (Fatemi et al., 2002). In ASD, this may cause suppression of the GABA-ergic system, resulting in heightened stimulation of the glutamate system, which has been associated with seizures. A positive intens autoantibodies reaction with GABAergic Golgi neurons of the cerebellum in 21% of children with ASD, were demonstrated, while no samples from non-sibling, typically developing children showed similar staining reaction (Wills et al., 2009), which in favor of the autoimmunity theory. Second, excitotoxic damage of neurons, possibly resulting from glutamate hyperactivity, may result in abnormal, structural development of the brain (Bittigau & Ikonomidou, 1997). The neurotransmitter serotonin has a wide range of affects on normal physiological functions including circadian rhythms, appetite, mood, sleep, anxiety, motor activity, and cognition. Serotonin is detected, not only in neurons of the nervous system but also in platelets and lymphocytes of the immune system, where it can exert dose-dependent, suppressive, or proliferative effects. In normal development, serotonin levels are high in the brain up to the age of five and then decrease dramatically (Muzik et al., 1999). Serotonin levels increase in the hypothalamus, hippocampus, and cortex in response to various cytokines, such as IL-1, IFN (Zhao & Schwartz, 1998; Simmons, & Broderick, 2005). Moreover, enzymes that control the conversion of tryptophan into serotonin are under the influence of IFN- and IL-1 (Wirleitner et al., 2003). Increased serotonin levels in peripheral blood platelets have been described in approximately one-third of patients with autism (Anderson et al., 1990). It is interesting that selective serotonin (5-HT) reuptake inhibitors (SSRIs) have been shown to be beneficial in treating obsessional and repetitive behaviors in some ASD patients sometimes (McDougle et al., 1996). The reason for the difference in serotonin levels is unknown; potentially, it may be a result of the presence of inflammatory cytokines or more likely, to alterations in the platelets themselves, which could modify serotonin uptake (Cook et al., 1996). In spite of the fact that imaging studies demonstrated a reduction in brain serotonin system. However, sometimes, treatment with SSRIs, produce a worsening of the symptoms. And accordingly, Azmitia et al., (2011), examined 5-HT axons that were immunoreactive to a serotonin transporter (5-HTT) antibody in a number of postmortem brains from autistic patients and controls with no known diagnosis who ranged in age from 2 to 29 years. Results from this study, demonstrated, a fine, highly branched, and thick straight fibers were found in forebrain pathways, such as, medial forebrain bundle, stria terminalis and ansa lenticularis. Many immunoreactive varicose fine fibers were also seen in target areas, for example, globus pallidus, amygdala and temporal cortex.

Morphometric analysis of the stained axons at all ages studied indicated that the number of serotonin axons was increased in both pathways and terminal regions in cortex from autism donors. Their findings, provide morphological evidence to warrant caution when using serotonin enhancing drugs (e.g. SSRIs and receptor agonist) to treat autistic children (Azmitia et al., 2011)

In addition, proinflammatory cytokines IL-1 and TNF are capable of affecting the activity of the serotonin transporter gene, a potential susceptibility gene in ASD (Coutinho et al., 2004). Cytokines and chemokines play a major role in many stages of development of the CNS and are known to induce the secretion of many neurotransmitters and neuropeptides (Biber et al., 2002). In turn, neuropeptides play an important role in all phases of immune system development, often acting as trophic factors, which has led to the hypothesis that neurotrophins (NTs) should be considered as neurokines, as they act in a cytokine like manner, influencing the development and function of the immune system (Levi-Montalcini et al., 1996). Several NTs with potent immunomodulatory actions, including neuropeptide Y, substance P, calcitonin gene-related peptide (CGRP), vasoactive intestinal peptide (VIP), BDNF, and NT-4/5, which have multiple affects on neurodevelopment and neuron maintenance, have been implicated in ASD. Analysis of neonatal blood spots by recycling immunoaffinity chromatography found that BDNF, VIP, CGRP, and NT-4/5 were elevated in ASD compared with typically developing control children but could not be distinguished from those with mental retardation (Nelson et al., 2001). Brain-derived neurotrophic factor is a major player in neurodevelopment known to regulate neuronal cell survival, growth, plasticity and differentiation, and is now considered to be a growth factor with a wide spectrum of functions outside the nervous system, including modulation and regulation of immune function (Vega et al., 2003; Nockher & Renz, 2003).

Based on animal studies, two structurally related neuropeptides, oxytocin and vasopressin, are believed to play a critical role in the formation of social bonding and recognition and in the processing of social cues (Young et al., 2002). Prairie voles are highly social animals, which form long-lasting pair bonds; in contrast, montane voles are asocial or solitary and do not form pair bonds (Wang et al., 1998). Central infusion of oxytocin in female or vasopressin in male prairie voles helps establish partner-bonding; this phenomenon can be blocked using specific antagonists (Williams et al., 1994; Young et al., 2001). Furthermore, oxytocin knockout mice have normal, cognitive abilities but diminished social recognition, suggesting a key role of oxytocin in social interactions. Other studies (Ferguson et al., 2000; Modahl et al., 1998) have found significantly lower levels of plasma oxytocin when compared with age-matched, normal subjects. Moreover, this decrease in oxytocin levels may be a result of a reduction in the processing of oxytocin, as increased levels of the pro-hormone form of oxytocin were found in autism patients (AL-Ayadhi 2005c; Green et al., 2001). In prairie voles, oxytocin and vasopressin receptors are located in the ventral forebrain, whereas the pattern of expression of oxytocin receptors differs in montane voles (Young et al., 2002). It would seem that not only the concentration of neuropeptides but also the pattern of receptor distribution may be important in the establishment of socially rewarding interactions. So far, signature patterns of neuropeptides and neurotransmitters and their respective receptors have yet to be established in ASD. Further studies that address this issue in ASD may provide clues into the development of impaired social interactions that are present in ASD. It is interesting that Dunzendorfer et al. (Dunzendorfer et al., 2001) have suggested a novel role for neuropeptides in the regulation of dendritic cell (DC) migration. They investigated locomotion of mononuclear cell-derived DCs at different

maturation stages toward gradients of sensory neuropeptides in vitro. Calcitonin gene-related peptide, VIP, secretin, and secretoneurin induced immature DC chemotaxis comparable with the potency of the chemokine regulated on activation, normal T expressed and secreted (RANTES), whereas substance P and macrophage-inflammatory protein-3 (MIP-3) stimulated immature cell migration only slightly (Dunzendorfer et al., 2001). Moreover, the neuropeptide VIP synergized with cytokines such as TNF-in the induction of DC maturation (Delneste et al., 1999). In the CNS, DCs have been found in normal meninges, the choroid plexus, and CSF and are actively recruited during inflammation, where they may play equal roles in the defense against infections and contribute to the break-down of tolerance to CNS autoantigens (Pashenkov et al., 2003). These findings suggest a central role for DC- and neuropeptide-mediated chemotaxis in the control of CNS inflammation and the generation of T cell reactivity against CNS antigens, and present an intriguing concept in the context of autism.

4. Conclusion

Autism spectrum disorder is a complex, neurodevelopmental, heterogeneous condition, with multiple phenotypes and subgroups that share behavioral characters. This natural complexity of the disorder has made the pathophysiology and consequently the etiology, exceptionally difficult. There is a considerable controversy in the literature regarding an immune-based factor in the search for pathophysiological cause in ASD. Nevertheless, with increasing reports of immune dysfunction in autism, there is a growing notion and concern that immune dysfunction may play a role in a subgroup of patients with ASD. Attempts have been made to link dysfunctional immune activity and ASD, such as maternal immune abnormalities during early pregnancy, increased incidence of familial autoimmunity, childhood vaccinations, and the generation of autism animal models based on immune parameters. Starting from the embryonic stage of life, to postnatal, and to adult hood, both neurological and immune systems are intertwined and abnormalities in one of them will be reflected on the other with dysregulation altering levels of cytokines, chemokines, neurotransmitters, neuropeptides, as well as hormones. Each of these substances may influence the course of development in the nervous and/or immune systems primarily or through secondary action. Moreover, while the extent to which many of the observations discussed herein are involved in the pathogenesis of autism is unknown, it cannot be discounted that immune dysfunction is an epiphenomenon or a consequence of the disease. Comprehensive extensive studies of autism and age-matched control individuals and their families are mandatory for more conclusive results.

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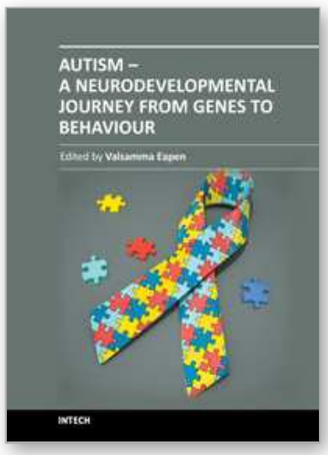

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The book covers some of the key research developments in autism and brings together the current state of evidence on the neurobiologic understanding of this intriguing disorder. The pathogenetic mechanisms are explored by contributors from diverse perspectives including genetics, neuroimaging, neuroanatomy, neurophysiology, neurochemistry, neuroimmunology, neuroendocrinology, functional organization of the brain and clinical applications from the role of diet to vaccines. It is hoped that understanding these interconnected neurobiological systems, the programming of which is genetically modulated during neurodevelopment and mediated through a range of neuropeptides and interacting neurotransmitter systems, would no doubt assist in developing interventions that accommodate the way the brains of individuals with autism function. In keeping with the multimodal and diverse origins of the disorder, a wide range of topics is covered and these include genetic underpinnings and environmental modulation leading to epigenetic changes in the aetiology; neural substrates, potential biomarkers and endophenotypes that underlie clinical characteristics; as well as neurochemical pathways and pathophysiological mechanisms that pave the way for therapeutic interventions.

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