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Various Infectious Agents Cause Immune System Dysregulation in Autism Spectrum Disorder

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Abstract

Autism spectrum disorder is a group of neurodevelopmental disorders that clinically presents in children as a lack of social interaction, restricted interests, and repetitive patterns of behavior. The most recent studies and publications demonstrate the enormous role of infectious agents and chronic inflammation not only in various comorbid conditions in these patients but also in the dysregulation of the immune system, which in turn leads to the accumulation of immunodeficiency states and to a worsening of the autistic phenotype. Therefore, the focus of this article is on how congenital and early postnatal infections found in children with ASD may trigger the chain of pathological events found in autism. We discuss how some infectious agents such as Toxoplasma gondii, measles, rubella, cytomegalovirus, Epstein-Barr virus, and herpes-simplex virus-1 and 2 are involved in the dysregulation of immunity and nervous system abnormalities. Furthermore, we want to provide recommendations for potential combined treatment methods for patients with autism with concomitant immune dysfunction.

Keywords: Autism spectrum disorder; Inflammation; Toxoplasmosis; Herpesviruses; Measles; Rubella; Immune dysfunction

Introduction

Autism spectrum disorder (ASD) is a group of neurodevelopmental disorders characterized by difficulty with social interaction, stereotypy, and restricted interests [1]. However, research and clinical observations revealed a range of other problems more related to the physical well-being of these patients. The association between ASD and various infectious agents, including herpesviruses, measles, rubella, and Toxoplasma gondii, was extensively described in the literature[2-6]. In addition, most publications in this field report a link between immune dysfunction and autism[7-10]. For instance, a case-series study involving 57 autistic children found that 35% of the participants had elevated levels of T-suppressor cells, while T-helpers, B-cells, and Natural Killer (NK)-cells were below normal[5]. Within the same cohort, more than 70% of children were Epstein-Barr virus (EBV) and cytomegalovirus (CMV) positive[5]. Furthermore, the same study found that rubella was present in about 60% of cases . Since many of the abovementioned infections are capable of establishing latency, subsequently altering and dysregulating the host's immune system, abnormality in the functioning of immunity in the infected patients should not be surprising. Indeed, ASD children were found to have chronically elevated levels of proinflammatory cytokines, chemokines, immunoglobulins M and G (IgM and IgG), as well as increased blood-brain barrier (BBB) permeability. The latter may be attributed to toxoplasmosis or other infectious agents that are brain-tropic. High BBB permeability makes the brain susceptible to the damage that low-grade systemic inflammation, exacerbating the autistic phenotype. Another strong contributor to the immune attack of the fetal brain is maternal autoimmune status. In fact, the case-control study [11]. Demonstrated the strong association between anti-fetal brain reactive antibodies in mothers and ASD diagnosis in their children, who were inevitably exposed to maternal IgG during intrauterine development. We also want to discuss how molecular mechanisms of innate and adaptive immunity are disrupted by the parasite Toxoplasma gondii as well as by the viruses like rubella, measles, CMV, EBV, and herpes simplex virus (HSV)-1 and 2.

Toxoplasmosis and Immune System Abnormalities

Toxoplasma gondii is an intracellular protozoan parasite that enters the host from the intestine with undercooked meat through the epithelial lining, where it infects macrophages and dendritic cells (DCs). This pathogen evolved to control the immune system via various pathways, enabling its survival. Although innate and adaptive immunity is activated to clear the parasite, it still possesses the capacity to regulate the production of some proinflammatory and anti-inflammatory cytokines. Specifically, infection of macrophages and dendritic cells with T. gondii leads to increased TNF-alpha production. Moreover, it elevates interleukin-10 (IL-10) and CCR7 expression, and the latter causes dissemination of the infection to other body sites with the infected macrophages[12]. Three major strains infect humans, type I, II, and III, both of which result in the activation of the NF-kB signaling pathway that in turn causes the production of IL-12 and IFN-gamma[13]. If cells are infected with strains II or III, interferon (IFN)-gamma upregulation leads to the cascade of STATs and IRG expression[13]. The latter surrounds and degrades parasitophorous vacuoles, while the former is a group of transcription factors involved in the initiation of expression of a broad range of proinflammatory cytokines [13]. The role of IFN-gamma is to hijack essential elements, particularly tryptophan, inside the infected cells to starve the pathogen [14]. However, in the case of type I, the downstream activation of STATs and IGR is inhibited by the virulence factors that this strain

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possesses; hence, the parasite survives[13].

The parasite initiates the migration of macrophages from the lamina propria to the distant organs. For instance, it reaches the brain by approximately the seventh day of infection, where it crosses the blood-brain barrier, but in healthy hosts, it remains laten[9] . In contrast, in immunocompromised individuals, the infection may be reactivated and cause life-threatening encephalitis. Furthermore, according to, the parasite's cysts have a modulatory effect on neurons, altering dopamine production. This essential neurotransmitter upregulation negatively impacts locomotion, memory, concentration, mood, learning, cognition, and overall behavior [15]. Furthermore, encephalitis caused by T. gondii results in reduced serotonin levels in the brain due to the fact the parasite causes the degradation of tryptophan, essential for serotonin synthesis [16]. Abnormal production of dopamine and serotonin was found to play a role in various psychiatric, neurodegenerative and neurodevelopmental disorders, and autism is no exception. Some clinical studies found a higher association between maternal Toxoplasma infection and the development of schizophrenia and bipolar disorders in their children in adulthood [17-19]. It suggests that the parasite had a more significant influence on the dopaminergic rather than serotonergic system. Moreover, this pathogen damages the normal structure of dendrites, leading to poor neuronal receptivity [20]. Additionally, T. gondii reduces the functionality of neurons and results in chronic activation of glial cells, creating a chronic inflammatory state in the brain[9]. The latter is the hallmark of ASD brains.

Role of Rubella in immune dysfunction

Rubella virus (RV) is a single-stranded plus-sense RNA virus that is transmitted via aerosol droplets, causing lymphadenopathy, cough, and flu-like symptoms in the infected patients[21]. The vaccination significantly reduced the incidence of this infection; however, mothers who were not vaccinated can get infected but remain asymptomatic, while their unborn children will be severely affected by the virus. RV may cause congenital rubella syndrome (CRS). In the case of CRS, the consequences for the fetus can be severe, resulting in sensorineural deafness, blindness, hepatosplenomegaly, and various brain defects [22]. In fact, it was determined that children born with CRS in the 1970s had a 200 times higher risk of developing ASD compared to the general U.S. population[23], which makes perfect sense considering the harm that CRS causes to the developing nervous system.

Moreover, the study by [21] showed that infecting cell cultures of mononuclear cells with rubella virus resulted in the increased production of TNF-alpha, IFN-alpha2, IFN-lambda1, and IFN-beta but not IFN-gamma. Furthermore, it was shown that after cells were infected with rubella, NF-kB signaling pathway activation was increased in response to bacterial lipopolysaccharide[21]. However, this persistently elevated immune response was found to be virus-specific because, despite this signaling pathway being upregulated in the case of rubella, rhinovirus had the opposite effect [24]. As seen from [21], rubella can cause overactivation of the innate immune system. All the problems mentioned above are often present in children with autism, which is not surprising because the issue of timely vaccination of the mothers against this virus with MMR (measles, mumps, rubella) vaccine persists worldwide. Notably, the 1976 study, which found that 39% of ASD children involved in the study had undetectable titers of antibodies against rubella despite being vaccinated[25]. This abnormality was not found in healthy vaccinated controls, suggesting that some autistic children cannot even form a normal immunological memory in response to vaccination. Since this infection still affects 5% of the global population because of a lack of access to vaccination in certain regions of the world and the vaccine may be ineffective in some population groups, the incidence of ASD cases with rubella positivity may continue to rise[6]. Hence, encouraging the administration of the MMR vaccine before pregnancy and making immunization widely accessible should become the priority for governments.

Role of Measles in immune dysfunction

If it were not for the MMR vaccine, many children would still get measles. Still, the measles virus (MeV) causes about 140,000 deaths annually among children under the age of five [26]. Neonates do not usually get the infection because they still possess maternal protection in the form of IgG against the virus. However, if toddlers do not receive timely vaccination, they are at high risk for MeV infection. MeV is capable of infecting immune cells and causing alteration in the functioning of the immune system of the host [27]. MeV entry into the macrophages and DCs results in the activation of the NF-kB signaling pathway, which in turn upregulates CD-150, the entry receptor for MeV, causing the release of proinflammatory cytokines like IL-12, IL-18, TNF-alpha, and IFN-gamma, as well as neutrophil-attracting chemokines[27]. Later stages of MeV infection are characterized by elevated levels of IL-4 and IL-10. The latter promotes wound-healing, immunosuppression, and delayed anti-viral response [27].

Fortunately, the MMR vaccine-related false publications about the possible association between ASD and MMR vaccines were retracted, but many parents remain cautious. It resulted in a drop in the vaccination rate and a subsequent rise in the incidence of these infections. If this trend continues, herd immunity may cease to exist, causing more MMR infections, which are dangerous for pregnant women and developing fetuses. Moreover, it is known that aside from IgG against MeV, IgG-immune complexes (IC) and IgG-IgE-IC can cross the placenta, resulting in severe atopy in neonates [27]. At the same time, the immune system of autistic children, most frequently dysfunctional from birth, may exhibit such phenomenon as antibody-dependent enhancement (ADE), which will be discussed later in the paper. ADE is observed during MeV infection and after immunization with the MMR vaccine, but it does not suggest causation. Instead, it indicates the importance of maternal vaccination and treating infections both in mothers and children.

Herpesviruses in Inducing Immune Dysregulation in ASD

Most human herpesviruses were found to have an association with ASD. In particular, HSV-1 and 2, EBV, CMV, and human herpesvirus-6 (HHV-6) were reported to play a role in immune dysfunction and behavioral problems in autistic children [2-4]. Indeed, herpesviruses evolved to utilize their hosts' immune system to remain latent and initiate replication only under favorable for the virus conditions, which is primarily an immunocompromised state of the host[28]. These viruses possess the ability to alter almost every aspect of human immunity, weakening it, causing autoimmunity, and leading to carcinogenesis in some cases.

Herpes Simplex Viruses

HSV-1 and HSV-2, which are prevalent among the global population, are capable of dysregulating the cellular immunity of their hosts. Specifically, HSV alters T-cell receptor signaling, inhibiting the NF-kB pathway but causing IL-10 overproduction, which suppresses anti-viral immune response[29]. It allows HSV to remain latent, especially in the central nervous system, particularly in the trigeminal nerve[30]. According to the study by, HSV possesses the capacity to suppress the innate immune response by downregulating IFN-alpha/

beta response, which is possible due to the HSV virion host shutoff (vhs) protein, which, as the name suggests, shuts off protein synthesis in the host and thereby inhibits innate immune system anti-viral response.

Cytomegalovirus

CMV is a beta-herpesvirus that infects from 60% to 90% of people worldwide [31]. It has the ability to establish a life-long latency after infecting a host and is capable of weakening the immune response to the virus [32]. At the same time, CMV is known to cause "memory inflation" with the overproduction of NK cells and CD8+ T-lymphocytes[33,34]. Specifically, CMV's m157-Ly49H binds to NK cells and results in their expansion; however, viral ULBP and MICA/B proteins restrict the expression of some important surface receptors of NK cells, essential for the activation of their anti-viral response[32]. Furthermore, CMV can reduce MHC presentation of viral peptides by DCs to T-cells, limiting T-cell response[32]. Still, when the latency is established, cellular and humoral response strengthens, producing anti-CMV antibodies and immune memory.

When it comes to congenital CMV, the consequences of this infection can be detrimental to a fetus. The viral infection may lead to sensorineural loss and a wide range of other neurologic problems in newborns exposed to CMV in utero[35]. When the immune system weakens, CMV may reactivate from its latency, causing further immune dysfunction and hence susceptibility to other infections and autoimmunity. When CMV infects autistic children, who have an array of issues with social domain and often other comorbid conditions, CMV-induced alteration of their immunity is an additional burden. Unfortunately, all the vaccines against CMV are still in the stage of clinical trials. Therefore, anti-viral therapy, including ganciclovir, foscarnet, valganciclovir, cidofovir, or letermovir[36], should be considered for CMV prophylaxis in ASD children and in mothers before pregnancy to prevent congenital CMV infection.

Epstein-Barr Virus

EBV belongs to gamma-herpesvirus and is known as the causative agent of infectious mononucleosis. Additionally, it is involved in the etiopathogenesis of human malignancies, including Burkitt's lymphoma, nasopharyngeal carcinoma, Hodgkin's lymphoma, T-cell lymphoma, and posttransplant lymphoproliferative disorder[37]. EBV infects almost everyone; thus, 90% of the global population has the infection, which usually remains latent[38]. The main target human cells of this virus are epithelial cells and B-lymphocytes, where EBV resides for a lifetime since it incorporates its DNA into the human genome, but these are not the only immune cells affected since macrophages and T-lymphocytes may be infected. More detailed mechanism of how EBV infects human lymphocytes, primarily B-cells, is described elsewhere[39]. This virus is highly successful due to its ability to escape the host's anti-viral immune response. Although the production of such proinflammatory cytokines as TNF-alpha, IL-6, IL-1-beta, IL-10, and IL-8 is initiated in response to EBV infection, the virus can suppress T-lymphocytes and NK-cells with its late membrane protein-1[40]. Furthermore, viral gp350 late protein induces overexpression of TNF-alpha[40]. EBV's role in tumorigenesis, particularly in B-cell lymphomas, is undeniable because it was shown to upregulate c-myc expression in B-cells, facilitating cell cycle progression and preventing apoptosis[37]. Thereby, malignant lymphoproliferation is determined by EBV-induced c-myc over-production, preventing B-cells from going to the resting G0 phase. Instead, monoclonal malignant B-lymphocytes expand in the cortex of lymph nodes, invading and destroying adjacent structures.

Even if the risk of carcinogenesis in ASD patients may not be high, this virus, having the capacity to infect monocytes, may cause brain changes over time[41]. Since BBB often has greater permeability in ASD children due to a persistently inflamed state, monocytes infected with EBV may enter the brain and cause mutations, structural alteration, and functional disruption in neurons or glial cells.

Dysfunctional immune system in ASD

When discussing the infectious nature of ASD, it is impossible not to mention the mechanisms of innate and adaptive immune systems disrupted in autistic patients. It was found that ASD is often characterized by low-grade chronic systemic and brain inflammation with such cytokines as IL-1, IL-6, IL-8, IL-17, and TNF-alpha being elevated[42]. Although direct causative pathways are yet to be found, recent research shows the worsening of psychiatric symptoms in patients with flare-ups of such autoimmune conditions as inflammatory bowel disease, multiple sclerosis, systemic lupus erythematosus, and some others [43]. This effect can be explained not only by the general state of feeling unwell and having debilitating signs and symptoms but also by the fact that inflammatory cytokines elevated in these disorders have a tremendous negative impact on brain function. Since many autistic children are exposed to maternal infections and inflammation during prenatal stages of development, it is unsurprising why many of them start to display signs of social domain abnormality early in life. For example, the Swedish study by [44]. showed a statistically significant association between maternal levels of C-reactive protein (CRP) as well as ferritin during pregnancy and later risk of development of ASD and attention deficit hyperactivity disorder (ADHD) or intellectual disability (ID) in their children. On the other hand, low CRP concentration accompanied by high ferritin levels in pregnant women was associated with ASD without ID or ADHD[44]. Hence, immune dysfunction in ASD is not a purely inherited problem but rather an interaction between genetics, epigenetics, and environmental factors, in most cases, HLA genes and infectious agents[45]. Indeed, according to [46] MHC class I plays an essential role not only in immune function but also in neuronal plasticity and memory formation. It suggests that prenatal disruption of these genes by the chronic inflammatory state can impair normal brain formation and development.

Cell-mediated and humoral immunity was found to be abnormal in ASD. Indeed, these patients have the shift of T-helper response to Th2 predominance, which explains frequent autoimmune comorbid conditions in autistic children[46]. Moreover, the high susceptibility of ASD patients to upper-respiratory tract infection could be explained by the low levels of IgA in children with autism[47]. It appears that in ASD, both innate and adaptive immunities are involved, characterized by elevated production of proinflammatory cytokines by macrophages, NK cells, T-cells, and abnormal B-cell function, resulting in a wide variety of autoimmune conditions and tissue damage in different organs from an overall inflammatory state.

A Possible role of Antibody-Dependent Enhancement in ASD

ADE of infection is a phenomenon in which the binding of a virus to suboptimal neutralizing or non-neutralizing antibodies causes its penetration into the immune cells of the infected organism and viral replication[48]. ADE is an inappropriate response to reinfection or vaccination. This phenomenon was described for such viruses as EBV, measles, influenza, HIV, dengue virus, coxsackievirus, murine CMV, foot and mouth disease virus, and some others[49]. ADE has

also been described for SARS-CoV-2, suggesting the involvement of ADE in the exacerbation of COVID-19[50]. In the case of reinfection or immunization with a live-attenuated vaccine, ADE may occur by one of the two mechanisms, extrinsic or intrinsic [49]. The former is caused by the excessive formation of immune complexes, modulating the immune response [49,50]. This mechanism results in the downregulation of the production of pro-inflammatory cytokines and type-I-IFNs, simultaneously upregulating IL-10 production, leading to immunosuppression [51]. The intrinsic mechanism occurs when non-neutralizing antibodies bind to Fc gamma receptor IIa on phagocytic cells and are internalized together with the virus, which replicates inside these cells [49, 50]. In the case of ADE, patients already exposed are likely to develop a more severe infection when exposed to a virus of another type than the first. Vaccine antibodies also appear to be responsible for an increased risk of severe disease in a naive person. Overall, ADE explains why parents and caregivers often report the onset of autistic phenotype after an infection or immunization. Children with ASD are exposed to maternal infections during their perinatal development; thus, their cellular and humoral immunity may be abnormal, which explains why instead of opsonization and neutralization of the pathogen or the formation of a long-term immunity in response to vaccination, they produce non-neutralizing antibodies that participate in ADE.

Recommendations for future therapies

The accumulated information shows that the role of infections in altering the immune system and neural circuits in ASD is practically impossible to deny. It leads us to believe that future therapies should include suppression of reactivation of the pathogens involved in the etiopathogenesis of the disease. Unfortunately, it is unknown in each specific ASD case if pathogen was acquired prenatally or postnatally. Still, treating ASD children for these infections, in addition to applying other conventional methods used for improving their social adaptation, may contribute to strengthening their immune systems and preventing further complications in the brain and systemically that occur as a result of chronic infections and inflammation. As mentioned previously, CMV can be treated with such therapeutics as valacyclovir, ganciclovir, valganciclovir, letermovir, and cidofovir[36]. Herpes simplex virus can be controlled with acyclovir and a while Epstein Barr virus can be treated with ganciclovir as well as 5-azacytidine and hydroxyurea showed promising results against EBV in clinical and pre-clinical trials, respectively[39]. Although, in adults, Toxoplasmosis is usually not treated unless symptomatic or immunocompromised, children under the age of 5 should always receive antiparasitic medications. Specifically, the most effective treatment to date is pyrimethamine combined with sulfadiazine or clindamycin[52]. Moreover, immunomodulatory agents can be included in the treatment regimen to not only eradicate the pathogen but also restore the normal functioning of the immune system in autistic children.

Conclusion

The involvement of infectious agents in immune system disruption and exacerbation of autistic phenotype is no longer a novel idea. Still, many aspects of this issue are yet to be understood. In this paper, we strived to summarize the impact of some human herpesviruses, measles, rubella, and toxoplasmosis on the immune system, which becomes disarrayed by various mechanisms pathogens utilize for survival inside their hosts. The future strategies of autism management should be focused on a multidisciplinary approach, which will incorporate evaluating patients for the presence of various infections with the subsequent combined therapy to target these pathogens.

Compliance with Ethical Standards

The study was funded by FLAASK, LLC.

The authors declare that they have no conflict of interest.

This article does not contain any studies with human participants or animals performed by any of the authors.

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