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Review Article

Neurovirological Aspects of Congenital Cytomegalovirus and Its Connection to Autistic Spectrum Disorder

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Abstract: Autism Spectrum Disorder (ASD) is a neurodevelopmental disease that includes a wide range of functional impairments, such as social and communication deficiencies, as well as limited and selective interest and behavioral patterns that are repetitive. Children with ASD often show developmental delay, which is noticeable at an early age, and show a wide range of symptoms that interfere with daily functioning, so early diagnosis includes early interventions. A complex set of genetic and environmental factors is associated with the development of ASD, which makes ASD a complex disorder, so there is a clear distinction between neurodivergent and neurotypical individuals. Since ASD is caused by a combination of certain genetic mutations and the prenatal/postnatal environment, we focused on the etiology of ASD in viral infections, i.e., Cytomegalovirus (CMV) as a possible cause of ASD. CMV is a neurotropic herpesvirus, which can be transmitted from mother to child during pregnancy. Cytomegalovirus (CMV) infection, which is often asymptomatic and can remain latent throughout life, can pose a danger to immune insufficiency individuals during pregnancy. CMV is the most common pathogen that causes intrauterine infections, is the most common cause of nongenetic sensorineural hearing loss in children, and the main cause of neurodevelopmental delay, so research suggests an association between congenital CMV infection with ASD and maternal seropositivity for CMV in pregnancy. spectrum in children. In the research, we used various online databases as sources for our study. The result of our research and processing of the given information indicates that maternal CMV infection in pregnancy is related to the development of autism spectrum disorders in children.

Keywords: Viral infections, Cytomegalovirus, Autism, Children

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1. Introduction

Autism spectrum disorders (ASD) are neurodevelopmental disorders characterized by impairments in two key domains: social-communicative and restricted and repetitive patterns of behavior, interests, or activities, as defined by the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-V). The severity of impairment in these two core domains has a major impact on how ASD manifests. In addition, clinical symptoms differ depending on whether or not there is an intellectual disability or a disability in verbal skills. ASD is one of the most common neurodevelopmental disorders affecting today's youth. It is expected that the number of children diagnosed with autism will exceed the number of children diagnosed with cancer, diabetes, and AIDS. ASD was the leading cause of disability in children under the age of five among all mental illnesses diagnosed in childhood. About 52 million cases of ASD were reported worldwide in 2010, with a prevalence of 7.6 per 1,000, or 1 in 132 people. In 2014, the Autism and Developmental Disabilities Monitoring (ADDM) Network in the United States predicted that one in 54 eight-year-olds had ASD, up from one in 150 in 2000 [1]. Increased public awareness, changed diagnostic standards, early diagnosis of autism spectrum disorders, and finding

adequate therapy, as well as focusing on its goals, are associated with an increase in the prevalence of ASD. Unfortunately, little is known about the causal process underlying this complicated condition, but genetic and environmental factors are known to have a major impact on ASD. ASD is also becoming increasingly apparent as a heterogeneous condition. Certain environmental conditions during critical periods of early neurodevelopment are associated with autism, specifically certain epigenetic factors, in addition to already complex hereditary variables. Prenatal exposure to numerous substances, including diseases and inflammatory processes in the mother, as well as perinatal and postnatal exposure to various chemical compounds, are becoming increasingly recognized as potential risk factors for the development of autism. An individual's susceptibility to viral infection can also be influenced by their genetic predisposition. Since the discovery of the link between autism and congenital rubella infections more than 50 years ago, a variety of additional infections have been discovered to be associated with the onset of autism. Viruses such as rubella, measles and mumps, polyomaviruses, CMV, and influenza have been associated with an increased risk of autism in epidemiological studies and case reports. Prenatal or early postnatal infections have also been shown, in animal experiments, to cause both acute and permanent neurological deficits and behavioral abnormalities in the offspring with symptoms similar to autism and schizophrenia. For example, respiratory infection with the human influenza virus in pregnant mice during the second trimester caused abnormalities in the development and behavior of the pups after birth, and the reason is the specific antiviral or immune response of the mother, which affected the development of the fetal brain [2].

Because inflammation and the dysregulation of cytokines and antibodies can significantly impact brain development, the potential role of immune dysregulation and autoimmunity in autism has received special attention. Immune dysfunction is a likely risk factor for the neurodevelopmental impairments seen in individuals with ASD. It has been suggested that viral infection can cause ASD through direct infection of the CNS, infection elsewhere in the body that can cause disease in the CNS, or changes in the immune responses of the mother or offspring. Various viral infections have been linked to ASD in many previous studies, however, some studies have not found a link. In this review, we summarize the accumulating evidence showing a possible link between viral infection and autism risk, which includes both human and animal studies.

2. Materials and Methods

In this research, we used various online databases, such as PubMed, Elsevier, Wiley Online Library, EBSCO, NCBI, and Neuroscience Online.

3. Viral infections and pregnancy

During pregnancy, women become more susceptible to infections. In order to protect the fetus, several mechanical and pathophysiological changes occur, as well as immunological adaptations. Infections can affect pregnant women more severely than non-pregnant women. Many common viral infections, such as cytomegalovirus (CMV) and herpes simplex virus 2 (HSV2), are asymptomatic and do not require hospitalization, unlike influenza (Figure 1) [3]. These viruses, although subclinical, still provoke an immune response. They also establish a delay in the expression of symptoms and can be reactivated during the host's lifetime. This means that women who are positive for CMV or HSV2 carry a dormant, i.e., insufficiently active, virus that can be reactivated at any time (Figure 2) [4]. Unfortunately, little is understood about how these viruses reactivate and affect the immune system of the mother, i.e., the host, but for now, clear evidence suggests that immunodeficiency is the main reason for the reactivation of these viruses (Yamamoto et al., 2013) [5]. During pregnancy, viral infections may or may not cause clinical indications in the mother. Viruses that have crossed the placental barrier and entered the fetus could

have catastrophic consequences for fetal development [6,7]. Because their CNS is not fully developed at birth or is still immature after birth, fetuses, and infants are at greater risk of viral damage. An unfavorable intrauterine environment caused by maternal viral infection during pregnancy significantly increases the likelihood of neuropsychiatric disorders such as ASD. Given the well-established teratogenic effects of prenatal infections, such as rubella and cytomegalovirus, on the CNS, it has been proposed that viruses may act as teratogens, leading to autism [8]. The incidence of ASD has been shown to be higher in pregnancies affected by a wide range of infectious agents in all trimesters of pregnancy, according to research [9]. In addition, the study found a relationship between hospital diagnosis of the disease and ASD and accompanying intellectual disability.

When an infection occurs, a number of cells from the innate and adaptive immune system are activated to help control and eliminate invading pathogens. Viruses can destroy neurons directly through cell lysis or by triggering apoptosis in them [10]. Through direct damage, death, free radical generation, cellular activation, and inflammation, the activation of innate and adaptive immune responses can ultimately lead to neuronal damage. Many studies have shown that systemic and neuropathic viral infections can cause neurobehavioral diseases like ASD [11, 12]. Chronic and progressive loss of structure and functioning of neurons in the CNS can occur as a consequence of neurodegenerative and neurobehavioral diseases (de Vries, 2019) [13].

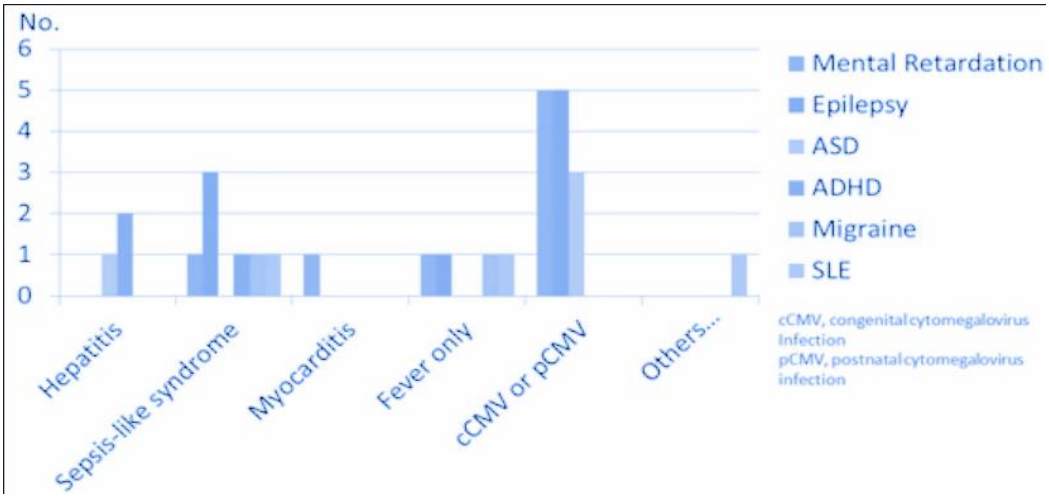

Figure 1. Congenital CMV and postnatal CMV in correlation with other pathophysiologies.
Source: (Chien-Heng Lin et al, 2021) [9].

During early fetal development, neuroinflammation can cause the psychopathological and neuropathological features of ASD. Neuroimmune variables, in fact, play a vital role in the etiology of neurological and neuropsychiatric diseases, especially those involving the early pathogenic onset of brain development. The fetal inflammatory response to intrauterine infection appears to play a role in infant brain damage and eventual neurological deficits [14]. Helper T-cells, also known as CD4 T-helper cells, are a type of T-cell that play a key role in the adaptive immune system by helping B-cells produce antibodies, induce macrophages, and recruit neutrophils, eosinophils, and basophils to sites of infection and inflammation. as well as the production of cytokines and chemokines. T-helper-17 cells are particularly essential for the immune response to external injury, and their dysregulation is thought to be at the root of many inflammatory diseases, including ASD (Liao et al., 2018) [15]. The generation and release of numerous cytokines during viral infection has a significant impact on immune and CNS cells due to receptor-mediated processes. Cytokines can be produced directly by the brain or they can penetrate the imma-

ture blood-brain barrier to reach the CNS (BBB). Interleukins (ILs) are a family of cytokines that are secreted in response to various inflammatory events, and they are the most likely culprits in embryonic brain development disorder [16]. In blood samples from patients with ASD, dysregulation of inflammatory cytokines including IL-1, IL-6, and IL-17, as well as immunomodulatory cytokines such as IL-2, was detected, highlighting the role of the immune response in the development of ASD [17–19].

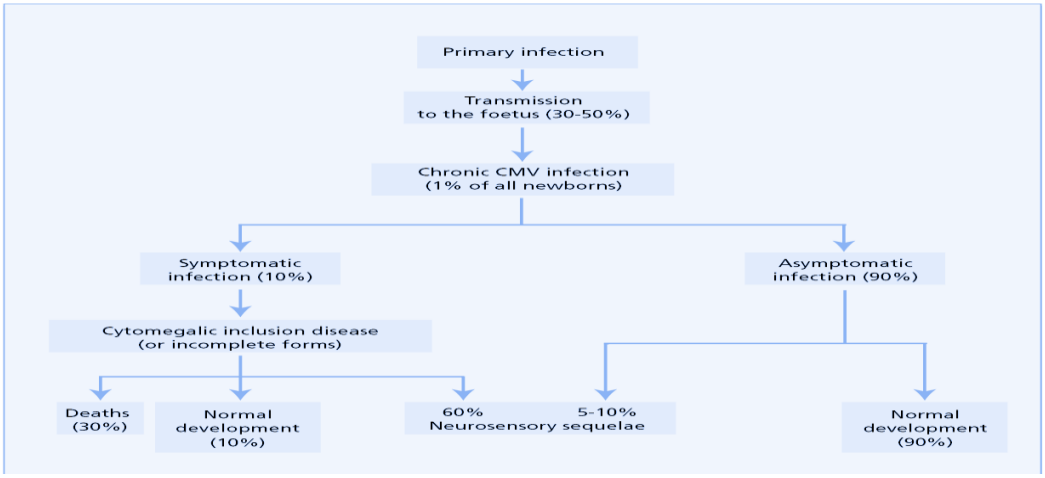

Figure 2. Algorithm of infection and consequences. **Source:** (M. R. Schleiss & Choo, 2006) [20]

Numerous studies have found that many ASD samples show inflammation-like conditions in the brain, cerebrospinal fluid (CSF), and peripheral immune system. Active cytokines, activated microglia, and astrocytes were detected in the brain of a person with autism, postmortem, indicating a state similar to inflammation [21–23]. An immune-activated state is established early and appears to be persistent in children with autism, as evidenced by increased cytokines in their CSF. An inflammatory-like state in the CNS may be associated with abnormalities in the peripheral immune system. It has been shown that IL-1, IL-6, IL-8, IL-12p40, and IL-17 are present in a higher percentage in the plasma of young children with ASD, i.e., these findings are associated with communication difficulties and abnormal behavior [24, 25]. In summary, the pathophysiology of ASD includes multiple genetic and immunological changes, such as an increase in inflammatory cytokines and an aberrant immune response. Maternal cytokines have been thought to dictate the type and severity of the immune response in pregnancy due to viral infection, and this may predict brain neuropathology based on the relationship between the inflammatory cytokine response and the degree of brain damage [26, 27].

4. Association of CMV with autism

Human cytomegalovirus (CMV) is the most complex member of the human herpesvirus family and is highly species-specific; it only infects humans. This virus is a member of the family of neurotropic beta-herpesviruses, which can infect epithelial cells, endothelial cells, smooth muscle cells, neurocytes, and sustentacular cells of the CNS (Figure 3) [28]. The virus enters the body through the epithelium of the upper alimentary, respiratory or genitourinary tracts, according to histopathological and immunohistochemical analyzes of necropsy tissues. It can be found in body fluids such as urine, saliva, tears, semen, milk, and cervical discharge, months to years after infection, reinfection, or reactivation, and may appear after the initial infection, reinfection, or reactivation [29–31]. Infants can become infected after infection from the mother through the placenta, during birth, or during breastfeeding. The predominant perinatal route of infection is ingestion of contaminated maternal vaginal secretions or breast milk. CMV can infect the CNS at any stage of development and maturation of the nervous system, leading to congenital or perinatal

infection. CMV infection or reactivation in the CNS can cause neurodevelopmental problems or other neurological diseases by interfering with the proliferation and differentiation of neural stem cells [32]

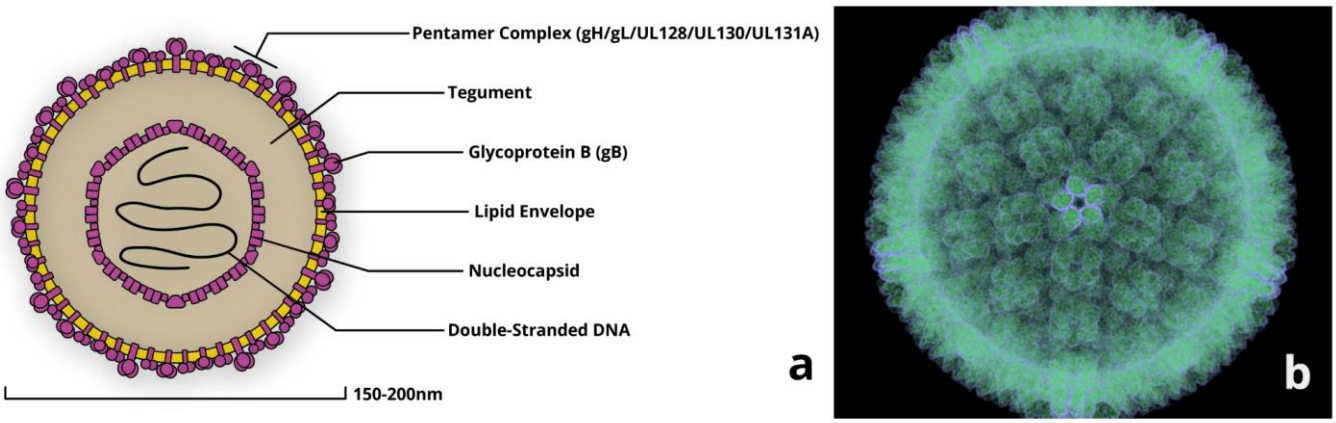

Figure 3. a) Simplified view of CMV. **Source:** Native Antigen b). Electron micrograph of CMV.). **Source:** Thermo Fisher

Only 11–17 percent of children have clinical indications at birth, but even if they are asymptomatic, they are at risk for developmental consequences (Figure 4). CMV can also be reactivated at any time during the life of the host [33]. When a latent virus is triggered by a combination of external and/or internal cellular stimuli, it enters the lytic phase of reproduction. The impact of viral reactivation on the maternal immune system, as well as the implications for fetal neurodevelopment and ASD, are still poorly understood. Prather et al. suggest that chronic maternal immune activation caused by persistent viral reactivation is caused by pregnancy-related stress and potentially harms fetal brain development [34]. If stress in pregnancy increases the chance of persistent viral reactivations in the mother, leading to chronic immune activation, this could have serious consequences for fetal brain development. If this is the case, as hypothesized by Bennabi et al., children born to mothers carrying these latent viruses will have more symptoms of ASD or suggestive of ASD than children born to seronegative mothers [35].

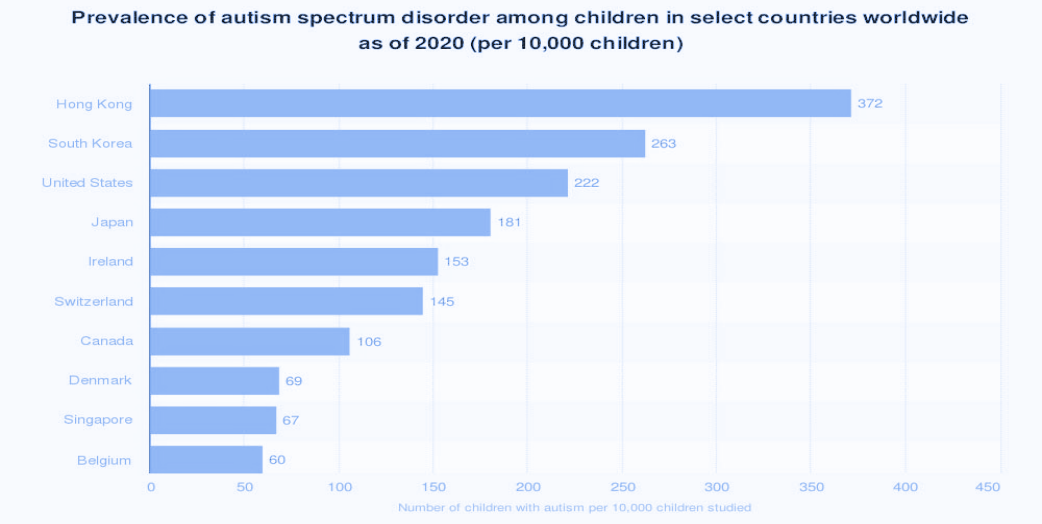

Figure 4. Prevalence of CMV in the world. **Source:** Stattista 2020

Herpesviruses cause inflammation by inhibiting the host's antiviral defense system by suppressing interferon. CMV infection has been shown to affect CD8 T-cell function, and maternal CD8 T-cell expression in the placenta may play a role in mediating perinatal brain damage [36]. CD8 T-cells, which include both cytotoxic effector and memory T cells, are adaptive mediators of immunity. To kill cells displaying a specific antigen, they release cytokines and other cytotoxic chemicals. Studies have shown that when decidual natural killer cells, which are mainly cytokine and chemokine producers, are exposed to CMV during pregnancy, they become cytotoxic effectors [37, 38]. In vivo, CMV has been shown to induce local infiltration of macrophages and T-cells, reduce trophoblast invasion and proliferation, and alter immune function.

Screening for CMV DNA in umbilical cord blood using (RT-PCR), instead of the gold standard method of detecting CMV in urine, in the first two weeks of life can detect congenital CMV infection early (Figure 5). Infants with CMV DNA had no abnormalities at birth, but a 12-month head MRI may reveal the presence of white matter lesions from the temporal to occipital regions. Developmental tests performed around the same time as MRIs in children with developmental delays revealed a link to congenital CMV infection. Children with congenital CMV infection who were previously asymptomatic, i.e., at birth, were later diagnosed with ASD. In high- and middle-low-income countries, seroprevalence increases with age and is higher in people with lower socioeconomic status. Seroprevalence in women of reproductive age varies depending on these factors. In the United States and Western Europe, seropositivity ranges between 50 and 85 percent.

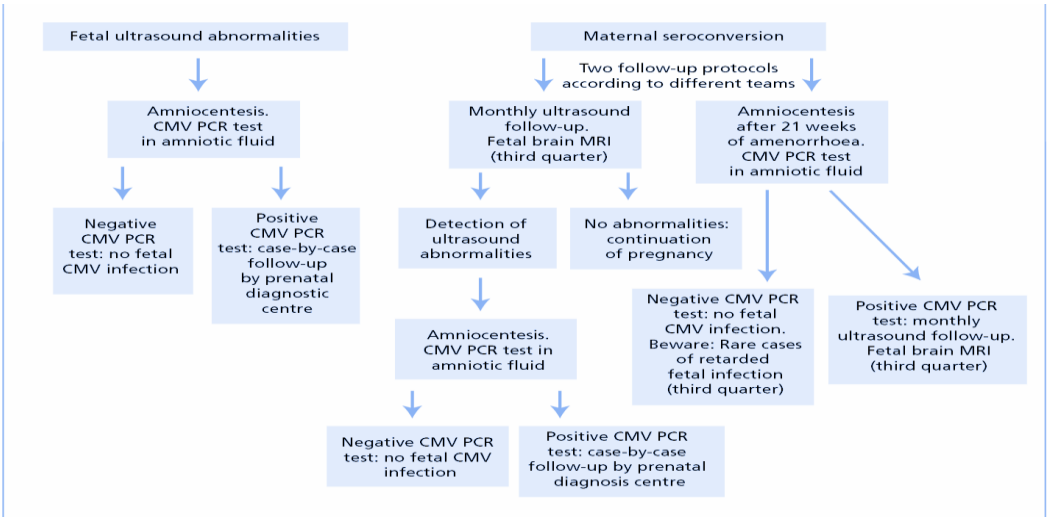

Figure 5. CMV testing algorithm in pregnancy. **Source:** (M. Schleiss, 2006) [39]

5. Conclusions

In a large number of studies, which we processed during our research, a clear connection between congenital cytomegalovirus and ASD is revealed, which indicates the seriousness of the problem of the viral infection itself, which has far-reaching consequences for the development of children. We emphasize that maternal immune activation, which involves dysfunction of the cytokine network, may be a potential pathogenic process linking viral infections to the risk of ASD. Research must continue to further understand the role of viral infection in the etiology of ASD.

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Conflicts of Interest: The authors declare no conflicts of interest.

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