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The Potential Link between Cytomegalovirus Infection and the Onset and Symptoms of Schizophrenia

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Abstract

Schizophrenia is a prevalent and severe mental illness commonly encountered by clinicians. The etiology of this chronic psychiatric disorder remains unknown. Still, evidence suggests a complex genetic and neurobiological basis that impacts early brain development, leading to a combination of psychotic symptoms such as hallucinations, delusions, and disorganization, as well as motivational and cognitive dysfunctions. Research investigating the potential link between Cytomegalovirus (CMV) infections and the development or causation of schizophrenia through antibody titer tests in serum and Cerebrospinal Fluid (CSF) analysis has produced varied and sometimes conflicting findings. Some studies have observed an increase in the level of CMV antibodies in the blood samples of individuals with schizophrenia, along with higher levels of CMV antibodies in the CSF compared to control groups. Conversely, several studies have indicated no significant difference in the levels of Serum or CSF CMV antibodies between individuals with schizophrenia and those in the control group. Some studies have suggested that exposure to CMV may lead to cognitive impairment and reduced neurocognitive performance, potentially contributing to the development of schizophrenia. The limitations of these studies include small sample sizes, non-rigorous methodologies, and a lack of diversity in ethnic and epidemiological investigations. Therefore, further research into the correlation between CMV and schizophrenia is necessary to gain insight into the etiology of these conditions.

Keywords: Cytomegalovirus • Schizophrenia • Psychotic disorders

Introduction

Schizophrenia is a prevalent and severe mental illness frequently encountered by clinicians in their practice. It presents both etiological and therapeutic challenges due to its characteristic psychotic symptoms and the often associated social and occupational decline. This chronic psychiatric disorder has a diverse genetic and neurobiological basis that affects early brain development, resulting in a combination of psychotic symptoms such as hallucinations, delusions, and disorganization, as well as motivational and cognitive dysfunctions [1,2]. It is important to bear in mind that around 1 in 10,000 adults experience the onset of schizophrenia annually, the rate ratio of schizophrenia occurrence in males compared to females is 1.4:1, and the median lifetime morbid risk for schizophrenia is estimated to be 7.2 per 1,000 persons. Moreover, the combination of population growth and aging has resulted in a substantial and growing disease burden associated with schizophrenia, especially in middle-income countries [3-5]. The viral hypothesis, which has been under serious consideration for over 70 years, suggests a potential link between viruses and the development of schizophrenia. Despite this, no specific virus has been conclusively identified as a risk factor for the disorder's origin. The idea that viruses or other infectious agents may be associated with schizophrenia or bipolar disorder dates back to the 19th century and has recently regained attention [6,7].

CMV is a prevalent beta human herpesvirus type 5, distinguished by its substantial genome of approximately 235 kilobases and around 250 potential protein-encoding open reading frames. Typically, CMV infects individuals asymptomatically during childhood, establishing life-long latency. The characteristic intra nuclear inclusions of cytomegalovirus infections were initially observed in 1881 by German scientists, who initially mistook them for protozoa. CMV disease manifests when there is a viral presence and a concomitant deficiency in immunity, such as in the case of immature foetuses, AIDS patients, and transplant recipients on immunosuppressive medications. Emerging evidence points to cytomegalovirus as a potential risk factor for the development of schizophrenia [8-10]. This study aims to evaluate the association between exposure to CMV and the development of schizophrenia by reviewing the current studies and evidence to provide better insight into probable correlation and etiologies.

Literature Review

CSF and serological studies

Research examining the link between CMV infections and the development or causation of schizophrenia through antibody titer tests in serum and CSF analysis has yielded varied and sometimes contradictory findings (Table 1). On the one hand, in particular studies, an increase in the level of CMV antibodies was observed in the blood samples of individuals with schizophrenia, along with higher levels of CMV antibodies in the CSF compared to control groups [11-20]. Additionally, there were significant differences in the levels of Immunoglobulin G (IgG) and Immunoglobulin M (IgM) antibodies between the schizophrenia cases and the control groups in these studies. The researchers found that untreated individuals with recent onset schizophrenia had significantly higher levels of serum and CSF IgG antibody to CMV compared to controls without psychiatric disease. Nevertheless, levels of serum CMV IgM class antibodies were not different. Treated individuals did not show significant differences in CSF antibodies to CMV compared to controls, but their serum IgG antibody levels were negligibly higher than those of controls. Differently, found marked increases in IgM antibodies to CMV in schizophrenia patients, regardless of whether they were on or off psychotropic medications. It is worth noting revealed a significant variance in CMV serum antibody titer compared to those of CSF in individuals with schizophrenia, as well as a difference in the CSF/serum CMV antibody ratio between patients and the control group. 68% of the patients exhibited an elevated CSF/serum antibody ratio exceeding 2 standard deviations above the mean of the controls, indicating localized antibody production in the central nervous system. The significantly elevated

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CMV antibody titers in the spinal fluid of groups of schizophrenic patients could potentially result from a suppression of serum antibodies resulting from treatment. Antipsychotic medications like chlorpromazine inhibit antibody production in vitro and the replication of CMV. However, to account for the increased CSF/serum ratios, it is assumed that the antibody suppression in the serum is more pronounced than in the CSF. This explanation seems unlikely due to chlorpromazine and similar drugs can cross the blood-brain barrier. An alternative and more compelling explanation for the low serum antibody titers is the suggestion that individuals at risk of schizophrenia may exhibit a diminished immunological response to CMV infection compared to the general population.

Table 1. Summary of main characteristics of CSF and serological studies of patients with schizophrenia. **Note:** (+) results means any sign of CMV antibody in CSF or Serum of tested subjects. (-) results mean negative results

Study	Country	Patients detail	Age range	Measurement	Results (±)
Albrecht et al., 1980	USA	Schizophrenic: 53 Control: 26	17-65 years	Neutralizing antibody assay	+
Gotlieb-Stematsky et al., 1981	Israel	18	20-61 years	Indirect immunofluorescence	-
Torrey et al., 1983	USA	Schizophrenic: 178 Control: 41	-	Enzyme-linked immunosorbent Assay (ELISA)	+
Kaufmann et al., 1983	USA	35 46	27-78 years	ELISA RIA	+
van Kammen et al., 1984 (5)	USA	27	-	ELISA	+
King et al., 1985	-	Schizophrenic: 20 control: 36	Mean: 39 Mean: 38.5	ELISA	-
King et al., 1985	-	Schizophrenic: 143 Control: 222	20-96 Years 15-86 Years	Enzyme Immunoassay (EIA)	-
Shrikhande et al., 1985	Ireland	Schizophrenic: 20 Control: 10	Mean: 46.9	ELISA	-
Schindler et al., 1986	Germany	Schizophrenic: 30 Control: 30	-	Interferon assay	-
Rimon et al., 1986	Finland	Schizophrenic: 40 Control: 40	Mean: 40.8 Mean: 44.5	Complement fixation	-
Delisi et al., 1986	USA	Schizophrenic: 38 (18 Female, 20 Male) Control: 17	Mean: 30 Mean: 34	Indirect immunofluorescence	+
Sierra-Honigmann et al., 1995	USA	Schizophrenic: 48	-	PCR-Enzyme Immunoassay (EIA)	-
Martin et al., 1996	USA	1 female	19 years	PCR	+
Fukuda et al., 1999	Japan	4 female 7 male	19-37 years	EIA	-
Leweke et al., 2004	USA	Schizophrenic: 38 Control: 73	Mean: 29.1 Mean: 28	Immunoassay	+
Novotna et al., 2005	Czech Republic	533 Male	19-21 Years	Personality test	-
Dickerson et al., 2006	USA	Deficit Schizophrenia: 88 Nondific Schizophrenic: 235 Control: 540	Mean: 43.3 Mean: 41.5 20-89 Years	Immunoassay	+
Kim et al., 2007	USA	Total: 447	-	EIA PCR	+
Niebuhr et al., 2008	USA	Schizophrenic: 180 Control: 532	More than 18 years	EIA	-
Shirtsa et al., 2008	USA	Schizophrenic: 329	Mean: 38.4	EIA	+
Krause et al., 2012	Germany	Schizophrenic: 31 (13 Female, 18 Male) Control: 31 (13 Female, 18 Male)	Mean: 36.5 Mean: 33.7	ELISA	+
Watson et al., 2013	USA	Schizophrenic: 680 Control: 283	Mean: 38.9 Mean: 40.8	ELISA	-
Li et al., 2013	USA	Cases: 855 Control: 1165	-	ELISA	-
De Witte et al., 2015	Netherland	Schizophrenic: 368 Control: 282	Mean: 30.5 Mean: 34.5	ELISA	-
Tanaka et al., 2016	USA	Schizophrenic: 28 Control: 28	-	EIA	+

On the other hand, several studies have indicated that there is no significant difference in the levels of Serum or CSF CMV antibodies between individuals with schizophrenia and those in the control group [21-30]. Interestingly, in some studies, the control group showed higher CMV IgG levels and greater CMV exposure compared to individuals diagnosed with schizophrenia. Reported a significantly higher CMV exposure in the control group, which remained significant even after adjusting for various potential confounding factors. These findings may seem counterintuitive but could be attributed to reduced CMV exposure in individuals with schizophrenia due to their more isolated lifestyle, a probable protective effect of CMV infection against the risk of developing schizophrenia, or indicative of altered immune function in schizophrenia [31-34]. In their study on US military personnel, observed that individuals with schizophrenia had notably lower levels of CMV IgG antibodies compared to matched controls, suggesting a potential association between higher CMV IgG antibody levels and a reduced risk of developing schizophrenia. The interaction of genetic and environmental factors may lead to immune dysregulation, with the absence of CMV IgG antibodies being a key factor. Activation of the immune system and prolonged neuro inflammation are well-established phenomena in the development and symptomatology of schizophrenia. While the autoimmune nature of schizophrenia is not fully understood, some studies indicate the possible involvement of autoimmune components in the pathways leading to schizophrenia. Given CMV's immunosuppressive effect, it may mitigate autoimmune damage and reduce the likelihood of developing schizophrenia in susceptible individuals with autoimmune reactions, which are potentially involved in the etiology and pathophysiology of schizophrenia. Therefore, individuals with similar vulnerabilities for developing schizophrenia who did not encounter CMV may be at a higher risk of developing the condition. CMV is also associated with a reduction in $CD4^+$ cells and their activation, followed by the production of proinflammatory cytokines, including TNF-α. TNF-α signalling through endothelial cells can alter the structure of tight junctions, leading to increased blood-brain barrier permeability and changes in brain structure and function, potentially contributing to psychiatric disorders such as schizophrenia.

Findings suggested that serological evidence of CMV infection is related to impaired cognitive function in these patients [35]. The researchers proposed that treating CMV-exposed schizophrenia patients with antivirals could potentially lead to improvements in cognitive function and clinical outcomes, irrespective of specificity to schizophrenia. However, investigating the use of adjunctive Val acyclovir to alleviate symptoms of persistent schizophrenia in CMV-seropositive individuals, no significant benefit of adjunctive Val acyclovir administration was observed in schizophrenia patients with persistent illness symptoms [36-40].

Considering all the results of serological studies previously mentioned, there is no sufficient evidence to confirm CMV as an etiology of schizophrenia or any direct association between them. The studies lack accuracy due to low sample size and study population, not precise methodology, and lack of ethnic and epidemiological diversity investigations.

Discussion

Brain studies

Several studies have suggested that exposure to CMV may lead to cognitive impairment and reduced neurocognitive performance, potentially contributing to the development of schizophrenia (Table 2) [41]. Discovered that male patients infected with CMV exhibited a reduced dentate gyrus size compared to CMV-positive females and the control group [42]. This result could be due to the detrimental effects of CMV on the granule cells of the dentate gyrus over an extended period [43]. Additionally, a Magnetic Resonance Imaging (MRI) study revealed that CMV-infected foetuses exhibited brain developmental abnormalities influenced by genetic and environmental factors, which may increase the risk of schizophrenia [44]. Furthermore, research on 69 schizophrenia patients showed that CMV IgG antibodies were present in those with reduced hippocampal size and weakened episodic verbal memory [45].

However, studies on screening several areas of the post-mortem brain, such as the orbital frontal brain, temporal cortex, and hippocampus from schizophrenia patients for evidence of CMV genome using molecular hybridization and Polymerase Chain Reaction (PCR) showed no sign of CMV DNA sequences in both patients and thereby refuting the hypothesis that CMV reactivation in the brain could cause schizophrenia [46-54].

Congenital CMV

Research indicates a direct link between congenital CMV exposure and an elevated risk of schizophrenia in offspring [55-58]. This association suggests that chronic maternal CMV infection impacts neonatal innate immune markers, potentially leading to deficient fetal immune responses and an increased risk of psychosis and schizophrenia. However, it is important to note that some studies have not found a clear relationship between congenital CMV and schizophrenia (Table 3) [59,60].

Table 2. Summary of main characteristics of brain and genetic studies of patients with schizophrenia. (+) results means any sign of CMV in the brains of tested subjects. (-) results means negative results

Study	Country	Patient/Samples	Age range	Measurement	Results (±)
Shearer et al., 1964	USA	1 Male	9 years	Intelligence test,	-
Aulakh et al., 1981	USA	Schizophrenic: 6 Control: 6	-	DNA hybridization	-
Stevens et al., 1984	USA	Schizophrenic: 15 Control: 9	-	Immunocytochemical staining of brain	+
Taylor et al., 1985	England	Temporal Cortex Tissue: 25 Temporal Lobe Tissue: 18	-	Dot-blot DNA hybridization	-
Carter et al., 1987	England	Schizophrenic: 20 Control: 20	22-84 Years 24-67 Years	Dot-blot DNA hybridization	-
Moises et al., 1988	England	Schizophrenic: 7 Control: 9	23-80 Years	Southern blot DNA hybridization	+
Alexander et al., 1992	USA	Schizophrenic: 8 Control: 8	-	PCR	-
Sierra-Honigmann et al., 1995	Germany	2 Schizophrenic male 1 Schizophrenic female control: 3	42 and 49 Years 35 Years age matched	PCR-EIA	-

Taller et al., 1996	USA and Germany	Schizophrenic: 31 Control: 23	-	PCR	-
Conejero-Goldberg et al., 2003	USA	Schizophrenic: 14 Control: 26	Mean: 39.9 Mean:48.7	PCR	-
Hoffmann et al., 2010	Israel	79 pregnant female	Gestational age 23-39 weeks	MRI	+
Houenou et al., 2014	France	Schizophrenic: 69 Control: 102	Mean: 39.4 Mean: 37.8	MRI	+
Andreou et al., 2020	Norway	Schizophrenic: 114 Control: 396	-	MRI, Solid-Phase immunoassay	(+) Male (-) Female

Table 3. Summary of main characteristics of studies on the association between congenital CMV and schizophrenia. (+) results means any positive effects of CMV on the brains of fetuses and newborns. (-) results mean negative results

Study	Country	Patient	Age range	Measurement	Results (±)
Buka et al., 2001	USA	Schizophrenic: 13 Control: 54	-	EIA	+
Dalman et al., 2008	Sweden	1.2 Million	0-12 years	ICD	+
Blomstrom et al., 2012	Sweden	Schizophrenic: 47 Control: 524	-	Immunoassay	+
Blomstrom et al., 2015	Sweden	Schizophrenic: 47 Control: 123	-	Immunoassay	+

Pathogenesis

CMV induces localized brain inflammation, leading to increased dopamine levels and potential behavioural changes such as schizophrenia. CMV is known to cause encephalitis and persist in the host's nerve ganglia. Reactivation of CMV may occur during periods of weakened immune function due to physical or emotional stress, potentially leading to schizophrenia symptoms. While the immune system of individuals with schizophrenia is typically not compromised, other mechanisms may be at play. Studies have indicated elevated levels of anti-Glutamic Acid Decarboxylase (GAD) antibodies in autoimmune conditions like type-1 diabetes and stiff person syndrome and have identified molecular mimicry between GAD and CMV peptides. Reduced GAD levels in post-mortem brain samples of individuals with schizophrenia may explain previous difficulties in detecting CMV DNA in such samples. Additionally, research has linked smaller temporal lobe sizes to schizophrenia symptoms [61-63].

Research suggests that schizophrenia may be associated with immune system dysregulation, as indicated by elevated levels of Interleukin (IL)-1β, Tumor Necrosis Factor (TNF)-α, and increased NF-κB activation. Additionally, signs of inflammation have been observed in the brains of individuals with schizophrenia. One potential mechanism through which CMV infections could impact immune function in the brain is by triggering tryptophan catabolism and increasing pro inflammatory cytokines. Tryptophan, an essential amino acid, can be metabolized into serotonin or other compounds through the kynurenine pathway, some of which modulate NMDA receptor activity and neurotransmitter availability. Activation of the kynurenine pathway has been implicated in the pathophysiology of schizophrenia. The precise ways in which altered tryptophan metabolism contributes to schizophrenia symptoms and tics are not fully understood. It is hypothesized that it may reflect immune system activation or that kynurenine and its metabolites could directly exert toxic effects in the basal ganglia and central nervous system. Further research is needed to elucidate the specific role of CMV as a potential factor in schizophrenia.

Conclusion

Numerous studies have investigated the presence of CMV in individuals with schizophrenia to determine if there is a discernible relationship between CMV and the disorder. Research exploring the connection between CMV infection and the onset or causation of schizophrenia, using brain tissue samples and antibody titer tests in serum and CSF analysis, has produced diverse and at times conflicting results. In light of the serological studies mentioned, there is insufficient evidence to establish CMV as a cause of schizophrenia definitively or to demonstrate a direct association between the two. The limitations of these studies include small sample sizes, non-rigorous methodologies, and a lack of diversity in ethnic and epidemiological investigations. Therefore, further research into the correlation between CMV and schizophrenia is necessary to gain insight into the etiology of these conditions.

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