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Review Article

Schizophrenia and Viruses: A Focus on Coronavirus Disease (COVID-19)

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Abstract

Viral infection appears to be a general risk factor for psychotic disorders. Coronavirus infection may also be a specific risk factor, conferring acute and long-term risk for psychosis. Even if the increased risk is marginal, the ongoing massive worldwide exposure to COVID-19 is likely to increase the incidence of psychotic disorders as Schizophrenia by a meaningful number of cases. This hypothesis is discussed briefly in this review article.

Key words: viral infection; COVID-19; schizophrenia

List of abbreviations:

CMV: Cytomegalovirus
COVID-19: Coronavirus disease
HSV: Herpes simplex virus.
SARS-CoV-2: severe acute respiratory syndrome coronavirus 2

Introduction

Schizophrenia is a severe neurodevelopmental disorder with genetic and environmental etiologies. The global prevalence of schizophrenia is ≅ 0.4% that represents a large burden to families and society. These patients also have high mortality rates and comorbid medical conditions (Rachel and S Fatemi , 2013).

A possible association between schizophrenia and the immune system was postulated over a century ago, and is supported by epidemiological and genetic studies pointing to links with infection and inflammation (Robert, 2004). Contrary to the traditional view that the brain is an immunologically privileged site shielded behind the blood-brain barrier, studies in the past 20 years have noted complex interactions between the immune system, systemic inflammation, and the brain, which can lead to changes in mood, cognition, and behaviour (Golam et al.,2015).

Pro-inflammatory markers of immune system activation have been widely recognized in schizophrenia, with evidence that schizophrenic patients may possess a hyper-active pro-inflammatory system as supported by increased levels of IL-6, IL-1β, and TNF-α in the sera of these individuals (Liu et al., 2010) as shown in Fig(1)

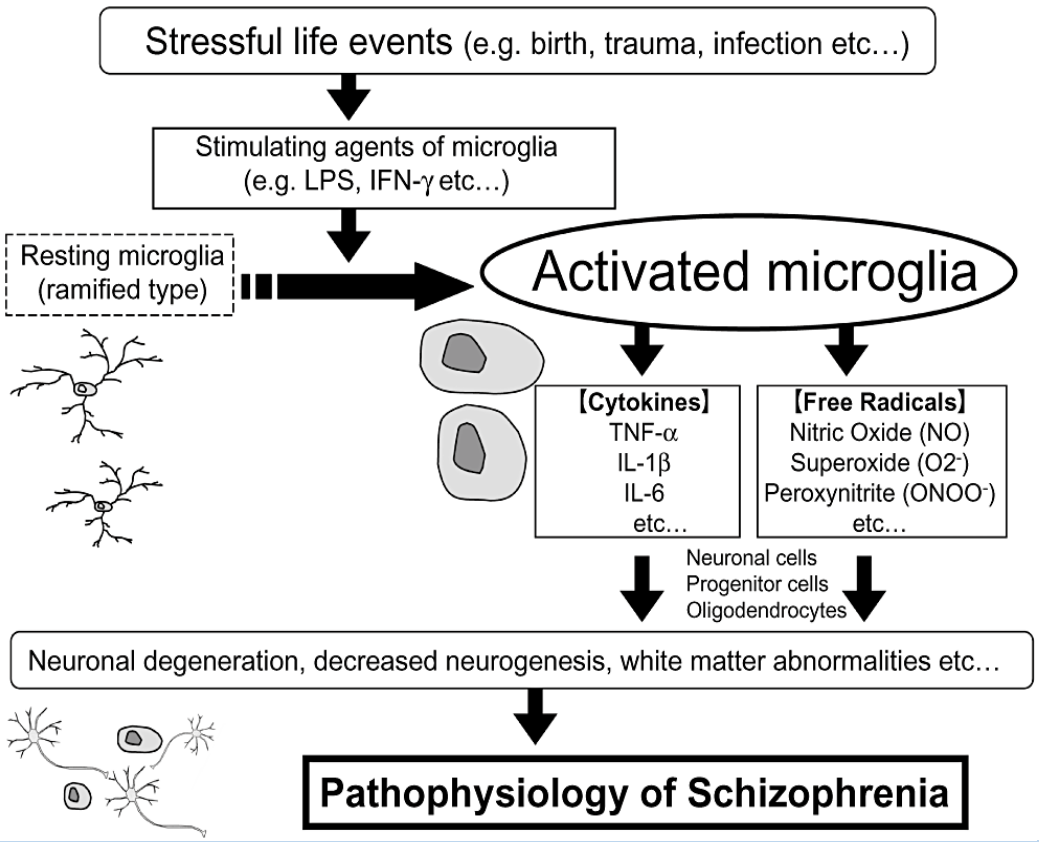

Figure 1: *Pathophysiology of Schizophrenia*

A viral hypothesis for the pathogenesis of schizophrenia has been under serious consideration for more than 70 years. To date, attempts have failed to identify a specific virus which contributes to the aetiology of the disorder (Anderson and Maes 2013).

The lysis of cells resulting from viral infection or immune recognition of infected cells is seen as merely one facet of a spectrum of pathogenic mechanisms which may be subtle and complex. This is particularly relevant to the central nervous and immune systems which share cell-surface receptors for various neuropeptides and neurotransmitters (Madje, 2010) as shown in Fig (2).

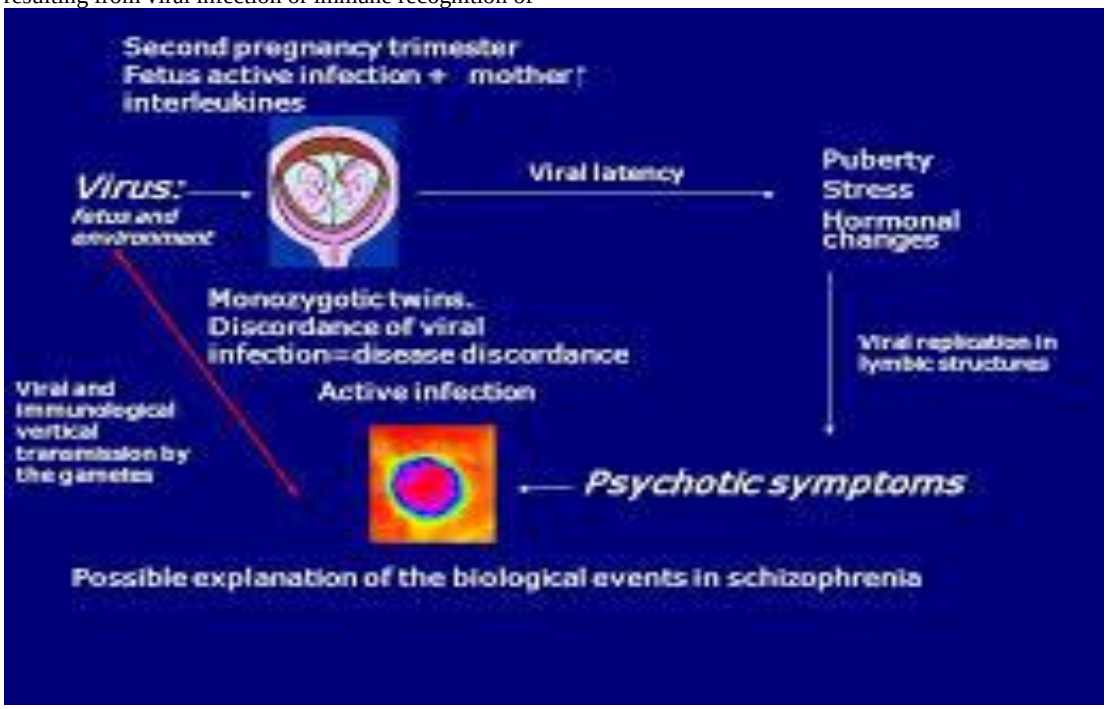

Figure 2: *Possible explanations of the biological events in schizophrenia*

Certain genes associated with schizophrenia, including those also concerned with neurophysiology, are intimately related to the life cycles of the pathogens implicated in the disease. Several genes may affect pathogen virulence, while the pathogens in turn may affect genes and processes relevant to the neurophysiology of schizophrenia (Jennie et al., 2019).

On other hand, numerous antipsychotic drugs are known to exert inhibitory effects on immune functions in general, and on pro-inflammatory cytokine networks in. Of special interest in the present context seem to be the recently identified microgliainhibiting effects of antipsychotic drugs. Hence, antipsychotic drugs may add to the therapeutic (or even preventive) effects in the pharmacotherapy of schizophrenia by dampening on-going inflammatory processes such as microglia over-activation (Mao et al., 2020).

1- Influenza virus

Influenza is a common infectious disease in humans, and it has been suggested that maternal influenza is an estimated risk factor for psychotic disorders, especially for schizophrenia (Carter, 2009)

There is epidemiological evidence suggesting an excess of winter births in patients with schizophrenia, indications of foetal insults in persons who develop schizophrenia and an association between foetal exposure to the influenza virus and the subsequent development of schizophrenia.

In the late 20th century, reports of a season-of-birth effect in schizophrenia were supported by large-scale ecological and sero-epidemiological studies suggesting that maternal influenza infection increases the risk of psychosis in offspring (Adrianna et al., 2020)

2-TORCH

TORCH pathogens (ie, Toxoplasma gondii, rubella virus, cytomegalovirus [CMV], herpes simplex virus) are known to be directly teratogenic, emerging evidence suggests that these infections represent the most extreme end of a much larger spectrum of injury .Infectious exposures can alter placental serotonin production, which can perturb neurotransmitter signaling in the developing brain (Benjamin et al., 2019).

Herpes simplex virus (HSV) has been implicated in schizophrenia as it has a tropism for the nervous system and is capable of replication in the brain. The ubiquitin ligase F-box protein 45 (FBXO45) is critical for synaptogenesis, neuronal migration, and synaptic transmission (Chenyao et al.2014).

Cytomegalovirus (CMV) may play an aetiological role in schizophrenia. Epidemiologically, both have a worldwide distribution and an increased prevalence in lower socioeconomic groups. Studies have reported that some patients experiencing initial episodes of schizophrenia have increased levels of IgG antibodies against CMV, but not other herpes viruses, in their sera and CSF(Fuller et al .,2006).

3- Coronavirus disease (COVID-19)

Coronaviruses are neuroinvasive, entering the brain *via* the olfactory neural pathway, and have been found in human brain tissue *post mortem* ***(****Rafael et al., 2020)*. COVID-19 may also be able to transmit placentally from mother to child *in utero* and directly impact foetal development **(Kimberlin and Stagno, 2020)**.

Although COVID-19 is predominantly a respiratory disease, it is known to affect multiple organ systems. SARS-CoV-2 affects the central nervous system and the brain function, behavior and cognition (David et al., 2020).

Maternal viral (and other) infections during pregnancy can affect the offspring, with greater incidence of neurodevelopmental disorders, such as autism, schizophrenia and epilepsy (Christos Pantlies et al., 2020).

There is some evidence that coronaviruses like COVID-19 can have acute and chronic impacts on neural development and function with links to psychosis (Zeng et al., 2020). Acute psychosis has been observed in individuals infected with SARS, a coronavirus similar to COVID-19 (Fuller and Robert, 2017).

The neurological signs associated with SARS-CoV-2 could be categorized in two types. In the first group, studies documented hyponosmia/anosmia and hypogueusia/agueusia in COVID-19 patients mildly affected by the virus and, therefore, not requiring respiratory assistance (Atefeh and Rahim, 2020).

On the other side, neurological signs like mental confusion (loss of bearings, disturbance of alertness), disturbance of higher functions, restlessness, or loss of consciousness have been principally reported in severe cases (Constant , 2020). Other neurological signs qualified as less common symptoms including headache, abdominal pain, diarrhea, nausea, and vomiting have also been reported (Lei el al, 2015).

In the most severely ill patients with pneumonia requiring intensive care, there appears to be additional severe inflammatory response and associated thrombophilia with widespread organ damage, including the brain (E Constant, 2020).

The hematogenous route of infection can directly affect the brain microvascular endothelium cells that integrate the blood-brain barrier and be fundamental in initiation of brain damage (Iván Alquisiras-Burgos et al.2020) as shown in Figure 3.

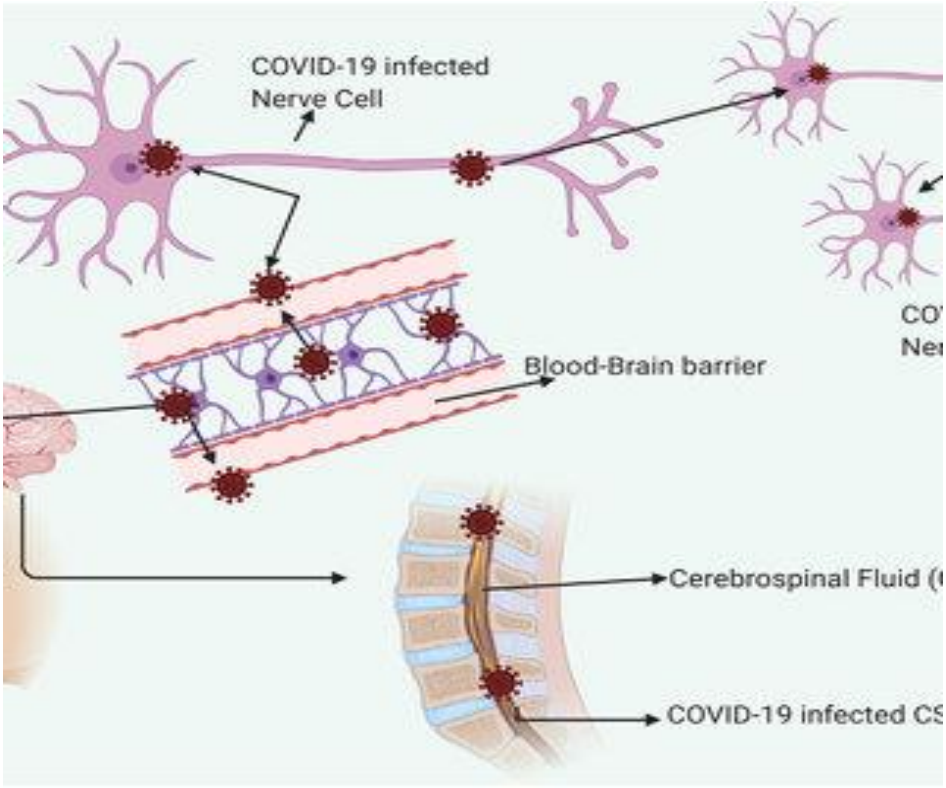

Figure 3. *Entry of Covid -19 into CNS*

Additionally, activation of the inflammatory response against the infection represents a critical step on injury induction of the brain tissue. Consequently, the virus' ability to infect brain cells and induce the inflammatory response can promote or increase the risk to acquire central nervous system diseases (Henry R Cowan 2020) Here, we contribute to the understanding of the neurological conditions found in patients with SARS-CoV-2 infection and its association with the blood-brain barrier integrity (Ivan et al.,2020).

High-titer anti-SARS-CoV-2 antibodies were detected in the CSF of comatose or encephalopathic patients demonstrating intrathecal IgG synthesis or BBB disruption (Chigr et al., 2020). A disrupted BBB may facilitate the entry of cytokines and inflammatory mediators into the CNS enhancing neuroinflammation and neurodegeneration. (Harry et al, 2020).

Schizophrenic patients are more susceptible to SARS-CoV2 infection, have worse clinical outcomes once contaminated, or have psychotic relapses in the context of the COVID-19 pandemic, there will be an additional burden to a system that is already pressed to the limit(Lais Fonseca et al 2020) .

Conclusion

Such preventive efforts could reduce the number of schizophrenia cases by as much as onethird, depending on which infectious agents were to be considered and what population studied. We need basic clinical research to understand developing of neurological disorders, translational and intervention research to improve their quality of life, and policy research to systemically prepare for their care.

Recommendation:

1- Health professionals and families should provide extra attention for the immunity of psychiatric patients through performing serological examination especially pregnant women.

2-Psychotherapy of schizophrenic patients should take in considerations the immulants including vitamin c and zinc pharmaceutical preparations.

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Conflict of interest:

The Author has declared that there are no conflicts of interest in relation to the subject of this work.

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