Review Article

Association between prenatal viral infections and the occurrence of schizophrenia in adulthood

Abstract

Aims Schizophrenia is a severe mental disorder that affects approximately 1% of the population worldwide. Genetics and environmental factors appear to contribute to the pathogenesis of schizophrenia. Epidemiological studies have focused on the relationship between viral infection during pregnancy and an increased risk of developing schizophrenia in offspring. The aim of our review is to summarize whether viral infections during pregnancy can lead to psychiatric disorders and especially to schizophrenia in adulthood.
Methodology A thorough search of PubMed was conducted and a review of the current literature. **Results** Epidemiological studies have focused on the relationship between viral infection during pregnancy and an increased risk of developing schizophrenia in offspring. Influenza virus, herpes virus 1,2 (HSV-1, HSV-2) cytomegalovirus (CMV), retrovirus, borna virus, are discussed as examples of viral infections associated with schizophrenia. These viral infections appear to interfere with the normal maturation of the brain and may lead to the subsequent onset of schizophrenia. Another epidemiological aspect of schizophrenia is the fact that it has a moderate prevalence of seasonal birth in winter and spring. It is also possible for an infection occurring in infancy to reactivate later, as is known to happen with herpes viruses.
Conclusions: Overall,Various studies showed that prenatal maternal infections appear to increase the risk of developing schizophrenia in the offspring, and this is due to the body's immune response to the infection, and not in exposure to specific viral or bacterial pathogens.

Keywords: pregnancy and viral infections, schizophrenia, congenital infections, viral infections and schizophrenia , prenatal viral infections

Introduction

Schizophrenia is a severe mental disorder characterized by cognitive disturbance. It affects approximately 1% of the population worldwide. The disorder has a diverse clinical picture and the first symptoms appear during puberty or early adulthood. People with schizophrenia may demonstrate various symptoms such as hallucinations, disorganized thinking, delusions, social withdrawal, and decreased emotional expression [1,2]. Additional

symptoms that can be seen in schizophrenia are sleeping and eating disorders, and an increased risk of co-morbidities such as obesity, diabetes, arterial hypertension, and coronary disease [3].

The causes of schizophrenia are mostly unknown. It is believed that genetics may play the main role in the onset of the disorder, due to its increased frequency among first-degree relatives. However, its appearance among monozygotic twins is approximately 50% which shows that environmental factors may play a role in the manifestation of schizophrenia and causing changes in the structure of the fetal brain increasing the risk of schizophrenia in individuals with a genetic predisposition [1,4]. The obstetric complications during labor, poor or inadequate prenatal diet, prenatal exposure of pregnant women to viral infections, the period of labor, labor in urban settings, smoking during adolescence are some of the environmental factors which may affect fetal brain development and lead to neurodevelopmental disorders which will increase the risk of appearance of schizophrenia in adulthood life [5-8].

Pathophysiology of schizophrenia

It is difficult to understand the pathophysiology of schizophrenia since its causes are not fully known.

It is thought that there is a disorder of the neurotransmitter system and mainly the dopamine system, which shows increased production and activity in the limbic system of the brain. The serotonin level is increased in these patients due to stress and block the dopaminergic neurons. The glutamine neurotransmitter presents reduced activity at the prefrontal cortex of the brain [9,10].

The neurodevelopmental disorder theory is supported by many researchers [11-15]. These disorders affect the temporal structures such as the hippocampus [12] which appears in the stages of prenatal development and many years before the onset of psychosis [11]. These disorders may affect the multiplication of neuronal cells and the formation of axial connections leading to insufficient development of the central neural system (CNS) (16) Brain CT and MRI findings showed enlargement of lateral cerebral ventricles and decreased

volume of cerebral cortex mainly in the frontal and temporal lobes, as well as reduced hippocampal volume [16,17].

According to the neurodevelopmental disorder theory both genetic and environmental factors play a significant role in abnormal cerebral maturation [18].

In the pathophysiology of schizophrenia, it seems that immune functions are disrupted due to increased activation of the immune system by viral or bacterial infections, or immunogenic factors. The increased activity of the immune system may lead to excess release of inflammatory cytokines, which in turn may affect CNS growth of the fetus [19,20].

Various studies have shown higher levels of proinflammatory cytokines during pregnancy [21,22]. However, the increased cytokines levels during gestation, such as TNF-a, IL-1b and IL-6 may adversely affect the development of the fetal brain [23].The cytokinesIL-1b, IL-6 and, TNF-a may cross the placenta, whereas they may be synthesized by the mother, the placenta itself, or from the fetus. The levels of these maternal cytokines have been shown to be elevated in human pregnancies in which the offspring exhibit schizophrenia [24,25]. Most likely, in both prenatal and postnatal infections, the risk of schizophrenia is rather increased by the immune response (inflammatory cytokines, discs), instead of the specific pathogen [26,27].

Environmental factors

Several genetic, psychological, and environmental factors have been implicated at the manifestation of schizophrenia. Epidemiological studies as well as studies from monozygotic twins show that the factors affect the premature development of the brain [28].

a) The season of childbirth

In their studies Hare *et al* and Machon *et al* reported that children who were born towards the end of the winter or early spring, showed an increased incidence of schizophrenia [29,30].

These findings correspond with other studies which showed that childbirths during these months showed an increased rate of occurrence of schizophrenia by 5% -15%. This is

happening probably due to an increase of incidence of viral infections during the winter and early spring period [31-33].

b) Stress during pregnancy

Situations creating intense stress during the pregnancy are associated with an increased risk of developing psychiatric disorders in the offspring due to the disturbance of the hypothalamic-pituitary-adrenal axis [34]. Maternal stress during the gestational period may cause placental vasoconstriction and delayed intrauterine growth of the fetus [35].

c) Poor nutrition

Various nutrient deficiency and especially of folic acid which is essential for cerebral development may lead to an increased risk of neurodevelopmental disorder [36].

d) Place of birth

The urban childbirth and upbringing of children are recognized as possible factors in the manifestation of adult schizophrenia later. Several mechanisms could explain this correlation, such as increased exposure to infectious agents in densely populated areas [37,38].

e) Obstetric complications

Various studies have shown that complications during gestation, or during labor and delivery may increase the risk of schizophrenia in offspring [39,40].

Most studies of the patients case-control showed a high rate of schizophrenia in people with complications during childbirth and especially in those with a genetic vulnerability [39,41-43]. This could be due to the hypoxia of the fetus which leads to irreversible injury of the hippocampus and of the amygdale [35,40].

Schizophrenia has also been linked to other complications of pregnancy such as low birth weight, [44] congenital malformations, small circumference of the head, suffocation during childbirth, uterine atony, perinatal bleeding, and ischemic injuries [45,46].

f) Prenatal viral infections

Viral infections during the 1st and the 2nd trimester of gestation can lead to neurodevelopmental disorders and possibly to the development of psychiatric illness during adolescence or adulthood [47-49].

1 Influenza

Infection with the influenza virus during pregnancy is a risk factor for appearance of schizophrenia in offspring during adulthood [31].

There are various studies showing that most people with schizophrenia are born during the winter months in late winter and early spring where flu outbreaks occur. There is much discussion as to whether direct offspring infection leads to neurodevelopmental disorders that ultimately lead to schizophrenia or whether this is due to the production of maternal cytokines in response to infection [30,32,50].

Mednick *et al.* examined the possibility whether the fetal viral infection is a causative agent of schizophrenia in adults. In their study, the included 1781 patients who were born during the flu A2 epidemic in 1957 in Helsinki and were diagnosed with schizophrenia. Their study showed an increased risk of schizophrenia among people whose second trimester of fetal life coincided with the flu epidemic, compared to those whose coincided the first or third trimester [51].

Another study by Limosin *et al,* compared 973 schizophrenic patients with a corresponding number of non-schizophrenic patients and their non-schizophrenic brothers. They showed that there was a association between exposure to influenza virus and the manifestation of schizophrenia. The number of schizophrenic patients who exposed to the flu virus, especially during the second trimester of pregnancy, was much higher than that of controls [52].

As for England and Wales, O'Callaghan *et al.* reported an 88% increase in schizophrenic adults which were born during the period from February to mid-March. The study included 616 patients which were born between 1983 and 1988 and suffered from schizophrenia. They divided them in two groups: patients with a family history of psychiatric disorder and patients without a family history. The study showed a significant increase only in

those who had no family history of any psychiatric disorder supporting the view that an environmental factor is responsible for the occurrence of this disorder [53].

Brown *et.al.* used serological methods to document prenatal exposure to influenza and the risk of schizophrenia. Their study included 64 patients who had been diagnosed with schizophrenia and 125 controls, all born during the period 1959-1966. Maternal serum samples were tested for influenza antibodies in order to estimate the prevalence in population during the same period. Serum samples came from pregnant women whose offspring developed schizophrenia compared with pregnant women whose offspring did not develop schizophrenia. The results of this study showed that the risk of schizophrenia increased in people exposed intrauterine to the flu virus during the first trimester of pregnancy compared to those in the second or third trimester [54].

Torrey *et.al*, on the other hand, examined birth data in 43,778 people with schizophrenia and compared them to 10,496,686 births between 1950 and 1959 in ten US states, and concluded that there was no significant increase in the schizophrenic birth rate just before during or after the 1957 flu epidemic [55].

2 Herpeviridae family

The exposure to herpes viruses is a possible risk factor for development of schizophrenia. Members of the herpeviridae family associated with schizophrenia include herpes simplex viruses (HSV) 1 and 2, cytomegalovirus (CMV), Epstein-Barr virus (EBV), human herpes virus 6 (HHV-6) and the varicella-zoster virus (VZV). Herpes viruses are not totally eradicated after their initial infection but remain dormant incorporated in host genome and are reactivated during immunosuppression [56].

3 CMV

CMV is found in saliva, blood, urine, vaginal fluids, and breast milk of infected individuals. CMV infection is transmitted through close personal contact and from mother to fetus. It is more common to be found among individuals with low socioeconomic status [57]. Maternal infection during pregnancy or reactivation of the virus leads to congenital infection of the

fetus. Congenital CMV infection is characterized by hepatosplenomegaly, jaundice, microcephaly, congenital mental retardation, hearing and vision loss, and cerebral calcifications [58,59]. CMV is the most common cause of damage to the fetal nervous system and, therefore, it is believed that there may be a causal link between congenital infection and schizophrenia [60]. Torrey *et al.* concluded that there is a positive causal relationship between CMV and schizophrenia [60]. Similar results were presented by Dickerson *et al* who studied 323 individuals with schizophrenia in whom elevated CMV antibody titers were found [61]. Albrecht *et al.* also reported elevated CMV antibody titers in 19 of 60 schizophrenic patients in cerebrospinal fluid [62]. On the other hand, several studies showed a negative correlation between CMV infection and schizophrenia [63-66].

Serum antibody titers against CMV were also studied from patients with schizophrenia. Those studies showed no significant differences in serum anti-CMV antibodies between schizophrenic patients and controls [64,67,68]. Additionally, increased levels of antibodies were also found in CSF IgM against CMV, but not IgG without being able to determine whether it was a primary infection or reactivation of the virus [69].

In a study by Hoffmann *et al*. a possible reduction in brain volume in CMV-infected embryos has been investigated by the use of MRI. The study included 27 CMV-infected embryos and 52 uninfected embryos. Infected fetuses had a significantly lower brain volume than controls. This, combined with a genetic predisposition, may increase the risk of developing schizophrenia later in life [70].

4 HSV

HSV is transmitted through nasal or oral secretions and can cause mild or no symptoms. The most serious complication caused by the virus is encephalitis with severe morbidity which can lead to psychosis and cognitive impairment [71].

Several studies have shown an association between HSV-1 infection and cognitive impairment in schizophrenia. However, no association was found between HSV-2, HSV-6, CMV, EBV, and VZV infection [72-74].

Similarly, a study by Brown *et.al*. examined whether maternal exposure to HSV-2 was associated with the risk of schizophrenia in adulthood. 60 prenatal serum samples were examined and the authors found no correlation between prenatal exposure to HSV-2 and the risk of schizophrenia [75].

Mohagheghi *et.al*. studied IgM and IgG serum titers against HSV-1, HSV-2, and CMV in 45 patients with schizophrenia and 45 controls. The results showed that anti-CMV and anti-HSV1 and anti-HSV2 IgG antibodies were significantly increased in patients with schizophrenia compared to controls [76]. Mortensen *et al*. studied the possible correlation between maternal exposure to HSV-2 and the risk of schizophrenia in their adult offspring. They examined the blood serum of 602 schizophrenic patients and 602 controls. The study showed an increased risk of schizophrenia in the offspring of mothers positive for serum HSV-2 IgG [77]. In another study conducted by Thomas *et al.,* they investigated whether intrauterine exposure to HSV-1 is associated with an increased risk of developing schizophrenia and reduced cognitive function. The study included 171 patients with schizophrenia, 27 with schizophreniform disorders and 100 controls. All were evaluated for exposure to HSV-1 using serum HSV-1 antibody titers. The results did not show a significant relationship between exposure to HSV-1 and the risk of schizophrenia. On the other hand, significant cognitive impairment was found among patients exposed to HSV-1 compared to non-exposed individuals [74].

5 EBV

Another virus that belongs to the herpeviridae family is EBV which can cause persistent infection. In the study by Dickerson *et al*., serum IgG EBV antibodies virus were measured in 432 people with schizophrenia and 311 controls. People with schizophrenia had elevated levels of antibodies to EBV viruses compared to the control population [78].

6 Retroviruses

Retroviruses are enveloped RNA viruses and exist as exogenous or endogenous entities. Exogenous retroviruses infect cells through a specific receptor for the virus, while endogenous retroviruses are present in the genome of host cells and are inherited through

successive generations [79]. A typical retrovirus contains 3 genes, the order of which is gag-pol-env [80] With the help of a reverse transcriptase, the viruses can convert their RNA into DNA, and this retroviral DNA can be incorporated into the cell of the host cell. Retroviruses are be able to induce immunodeficiency and neurological disorders such as multiple sclerosis and schizophrenia. Human endogenous retroviruses (HERVs), which belong to the human family of endogenous W-type retroviruses (HERV-W), have attracted the most attention. Several studies have since then investigated whether there is a causal link between HERV and schizophrenia, with the HERV-W family showing the greatest correlation indications [81].

In their study, Huang *et al* collected blood samples from 58 individuals with schizophrenia and 38 controls. Using RT-PCR, they examined the RNA levels of the HERV pol gene in the blood. Retroviral pol genes were found to be elevated in 20 out of 58 subjects with schizophrenia. Additionally, the Western blot method showed elevated antibodies against ERV9 pol protein in the serum of the patients with schizophrenia and HERV+, but not in controls leading to the conclusion that the activation of certain retroviral proteins of the HERV-W family in some patients can lead to schizophrenia [82]. In a different study, the same group tried to detect genes with mRNA sequencing similar to the human endogenous human gene HERV-W env in the plasma of 118 subjects with recent onset of schizophrenia and 106 physiological controls/The authors detected the gene in 42 out of 118 individuals with schizophrenia but none was found in the participants of the control group of the study. Using human glioma cells U 251, they found that HERV-Wenv overexpression regulates the neurotrophic factor derived from the brain (BDNF), a gene associated with schizophrenia, the N2-receptor receptor type of neurotrophic tyrosine kinase type 2 (NTRK2, also known as TrkB) and dopamine receptor D3 and increased cAMP phosphorylation. Gene tests showed that HERV-W env activates BDNF production in human U251 glial cells. The HERV transcriptional activation is associated with the development of schizophrenia in some patients, and HERV-W env regulates the expression of schizophrenia-related genes [83].

Retroviruses incorporate into DNA and can infect brain cells, and causing damage to brain function, combined with genetic factors. Yolken *et al.* investigated the expression of RNA using the RT-PCR method in the frontal cortex in the postmortem brains of four

individuals with schizophrenia, four subjects with bipolar disorder, and six subjects control group. HERV-W expression was increased significantly in subjects with schizophrenia compared with control participants [84]. Perron *et al*. in their study quantified HERV-W gag and envelope (env) proteins in the serum of 49 subjects with schizophrenia and 49 healthy individuals, with a dedicated immunoassay set-up with specific monoclonal antibodies to either antigen. A positive antigenemia for envelope protein was found in 47% of patients, while 49% of patients had a positive antigen for gag compared with 3% for env and 4% for gag in the healthy subjects. A significant correlation was also found between gag or envantigenemia and C-reactive protein, suggesting a pathophysiology caused by inflammation [85]. Karlsson *et al*. identified similar nucleotide sequences in retroviral pol genes in CSF in 10 of 35 patients (29%) diagnosed with schizophrenia and schizophreniform disorders with recent onset, as well as in CSF of one out of 20 subjects with chronic. These retroviral sequences which are mainly related to the HERV-W family were not detected in any of the 32 participants in the study. Moreover, in the same study, brain tissue was taken postmortem from the frontal cortex of 5 subjects with schizophrenia. Additionally, similar frontal cortex tissue was obtained from six individuals with no history of psychiatric illness. Increased RNA transcription was found for retrovirus HERV-W in the brain tissue of individuals with schizophrenia compared with the healthy ones [86]. Yao *et al.* reported elevated transcription levels of HERV-W gag in mononuclear blood cells obtained from 30 patients with psychosis, including schizophrenia, schizophreniform disorder, and schizoaffective disorder compared to 26 healthy subjects in the control group. Increased levels of HERV-W gag were observed, but no difference was found between HERW-W env transcription levels [87].

7 Borna virus

Bornavirus (BDV) is a negative ss RNA virus that belongs to the Bornaviridae family, and naturally infects horses, sheep, poultry, and cattle. It is a neurotropic virus that infects the brain and can cause nerve cell degeneration in the chronic phase of the disease [88]. BDV infection of CNS in animals can cause sporadic neurological diseases such as encephalitis, meningitis, and various abnormalities in movement and behavior, and sometimes with

psychological manifestations similar to schizophrenia [89]. Several studies have focused on whether BDV disease can cause psychiatric disorders in humans such as schizophrenia and depression. Most studies have not shown that BDV infection causes psychiatric manifestations in humans and especially the manifestation of schizophrenia.

Yong *et al* showed in their study that BDV infection may in some cases be associated with schizophrenia [90].They measured BDV p24 antibodies in the sera of 116 schizophrenic patients and control subjects, and the results showed that infection is possibly associated with schizophrenia [90].

The study of Iwata *et al*, however, showed opposite results. BDV p24 RNA was measured in monocytes of the peripheral blood (PBMCs) of psychiatric patients, 49 of whom had mood disorders, 77 schizophrenia, and 84 control individuals. The results did not show a greater prevalence of BDV p24 RNA in patients with psychiatric illness compared to the control group. Similar results were found by the study of Selten *et al.* who showed that the role of BDV infection in the pathogenesis of schizophrenia is unlikely [91,92]. The same negative correlation was shown by a study conducted in Iran, where the possibility of BDV infection-causing psychiatric disorders was considered. They examined samples of peripheral blood for the detection of BDV RNA nucleoprotein P40 from120 patients (60 with bipolar disorder (BD) and 60 with schizophrenia) and 75 controls. The results showed no link between BDV infection and the pathogenesis of these psychiatric disorders [93]. In another study, which included 40 individuals with the first onset of schizophrenia and 40 controls, the researchers examined whether there was a correlation between BDV infection and schizophrenia measuring BDV RNA in PBMCs isolated from patients with the first onset of schizophrenia. The results did not show a causal link between the Bornavirus and schizophrenia [94].

8 Other viral infections

A small study by Severance et al. in 106 patients with early onset of psychotic symptoms and 196 controls showed a higher seropositivity for HKU1, NL63 and OC43 coronaviruses [95]. A possible role of parvovirus B19 infection has also been implicated in some studies, but the results should be further investigated in larger studies [96,97].

Eagles in an early paper in 1992 suggested a possible connection between poliovirus infection and schizophrenia, but his hypothesis was never tested [98,99]. A possible role of Zika virus infection has been proposed in the pathogenesis of schizophrenia but there are no data supporting this hypothesis [100,101].

Conclusion

Results from various studies show a positive association between viral infections during pregnancy and subsequent development of schizophrenia in offspring. Prenatal viral infections can change the normal development of the unborn baby's nervous system through the activation of the maternal immune system.

Prenatal maternal infections appear to increase the risk of developing schizophrenia in the offspring, and this is due to the body's immune response to the infection (increased levels of inflammatory cytokines, antibodies), and not in exposure to specific viral or bacterial pathogens.

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