

Revisiting Old Ghosts: Prenatal Viral Exposure and Schizophrenia

Rael D. Strous MD¹ and Yehuda Shoenfeld MD²

¹Beer Yaakov Mental Health Center, Beer Yaakov, Israel

²Research Unit of Autoimmune Diseases and Department of Medicine B, Sheba Medical Center, Tel Hashomer, Israel

Both affiliated to Sackler Faculty of Medicine, Tel Aviv University, Ramat Aviv, Israel

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Schizophrenia, affecting 1% of the population worldwide, consists of a constellation of symptoms with clusters of positive symptoms, negative symptoms and neurocognitive dysfunction. While research into the pathophysiology of the illness is developing at a rapid pace, success remains limited and the search continues for a deeper understanding of the causes. What accounts for the heterogeneity of schizophrenia still remains unknown, and there may be several etiologies accounting for the phenotypic expressions of the illness that may include aspects of both nature and nurture, i.e., a two-hit hypothesis encompassing factors of genetics and environmental insult with clinical subtypes of the illness potentially reflecting sub-mechanisms of the disease [1].

Prenatal viral infection hypothesis

One such hypothesis is the strong body of evidence implying the role of an infectious agent in the etiopathology of the illness. While first proposed in the 19th century (1845) by Esquirol, it was Mednick et al. in 1988 [2] who provided strong epidemiologic data suggesting that it is prenatal viral influenza infection in the second trimester of pregnancy that leads to schizophrenia illness later in life. This landmark study was carried out in a Finnish cohort whose mothers were exposed to the 1957 influenza A2 epidemic. Close to 30 articles have attempted to verify and expand the prenatal viral infection finding, with mixed results [3,4]. The discrepant findings may be explained in several ways. These include the difficulty in precisely measuring maternal exposure of individuals with schizophrenia, difficulty in lengthy retroactive report requirements (maternal recall), lack of sophisticated means to confirm previous exposure (e.g., virus may induce infection and then disappear, or infection may be secondary to some as yet unknown virus), misclassification error, and poor statistical power.

Evidence for the theory

Much of the *in utero* viral infection theory has been based on season of birth (winter and early spring) [5] since viruses infect the central nervous system more under “cold conditions,” as well as the observation of an increased incidence of schizophrenia in urban areas in which individuals are more susceptible to viral infection based on crowding, exposure, etc. [3,6]. Furthermore, the fetus is vulnerable to “ascending infection” following obstetric complications (more common in schizophrenia) [7] and the fact that an immature brain may not offer sufficient protective immune

response against the virus or its damaging toxins. This process may occur despite the absence of serologic evidence of infection at birth since the immunoglobulin response is slow to develop during gestation and may even function subnormally at birth [1]. Infection would be expected to affect neurodevelopment and delayed illness onset through neurotropism, latency, and abnormal neuronal circuit formation [8].

Despite the initial enthusiasm of the scientific psychiatric community to the early reports, the theory largely fell out of favor due to a lack of robust convincing evidence [9]. However, more recently the theory has attracted revived and resurgent attention due to technological advances in the areas of neuropathology, molecular biology and immunology investigation. Much of the subject matter relating to evidence suggesting an association between prenatal influenza exposure and schizophrenia is comprehensively reviewed by Ebert and Kotler in this month's issue of *IMAJ* [10].

Unanswered questions and possible considerations

Several questions remain unanswered. First, if a virus is involved in intrauterine infection, what is the type or nature of the virus? While several studies have indicated the involvement of the influenza type A virus [10,11], several others have proposed associations with rubella, measles, varicella zoster, coxsackie B5, polio and diphtheria [2,11–13]. Congenital rubella with schizophrenia-like symptoms, for example, exhibits signs of enlarged ventricles and decreased cortex gray matter, signs well known to be associated with schizophrenia [14]. A particularly interesting alternative consideration comes from fairly recent data showing evidence of infection with retroviruses in schizophrenia [15], important since many endogenous retroviruses are differentially active during fetal development [16]. Brain retroviral activation and reintegration occurring during prenatal stages may result in delayed brain function alteration [17]. A further intriguing possibility is a synergistic combination of two or more viruses required to induce the insult leading to schizophrenia (for example, both hepatitis B virus and delta agent are required for hepatitis delta).

Second, what is the nature of the insult caused by the virus? Recent investigation in a rat animal model demonstrated that maternal viral infection led to several “highly abnormal behavioral responses” in offspring reaching adult stage. These included deficits of prepulse inhibition in the acoustic startle reaction, robust

responses to antipsychotic and psychomimetic drugs, deficits in exploratory behavior, and impairment in social interaction [18]. All of these paradigms are used as models for behavioral and neurocognitive deficit in schizophrenia. Furthermore, in rats after maternal viral influenza infection a range of neuropathologic findings has been observed including neocortical and hippocampus thinning, reduced Reelin immunoreactivity levels, pyramidal cell atrophy, variations of neuronal nitric oxide synthase expression, and macrocephaly [19–22]. Additionally, aberrant neuronal migration has been noted [23]. All of these findings may have relevance to schizophrenia; however, definitive evidence remains elusive at this stage.

Third, if a virus is the offending agent associated with schizophrenia, how does the virus effect its damage? This question is particularly relevant since the influenza virus appears only rarely to cross the placenta, viral antibody staining of neonatal rat fetal brains is negative, no encephalitis is noted [18], and non-lethal strains of influenza virus are usually restricted to the respiratory tract. Therefore, an indirect effect of the virus on fetal brain development is a more likely etiopathologic scenario. Despite one investigation noting intracytoplasmic encapsulated particles similar to herpes virus in postmortem schizophrenia tissue and brain tissue of fetuses born to mothers with schizophrenia [24], recent reports suggest that it is not the virus itself that effects the damage, but rather influenza antibody. Brown and co-workers [4] demonstrated serologic evidence that prenatal influenza increases schizophrenia risk sevenfold. The authors hypothesize that it is maternal immunoglobulin G antibody that crosses the placenta and cross-reacts with fetal brain antigens by means of molecular mimicry. This would adversely affect fetal neurodevelopment and increase later vulnerability to schizophrenia. The process of injury may also occur following the eliciting of an autoimmune response to the viral intrusion by means of homology between a pathogen and host protein with production of auto-reactive antibodies [25]. In addition, prepulse inhibition deficits have been noted in the young pups of rat mothers that were infused with a substance – synthetic double stranded RNA poly(I:C) – which induces an antiviral-like immune response without viral infection itself [18]. A further proposed mechanism is that of maternal cytokines, produced in response to maternal viral infection, which may cross the placenta and similarly lead to impaired neurodevelopment [26], such as with periventricular leukomalacia [26], cerebral palsy and mental retardation [28].

Fourth and finally, at what stage does the hypothesized viral infection take place? While it has generally been believed that the maternal infection transpires during the second trimester, based on serologic evidence of serial archived blood from mothers with children with schizophrenia, Brown et al. [4] found that the infection exposure most likely occurs during the first trimester.

Associated non-specific factors

While the above findings appear fairly convincing, it should be remembered that many other secondary non-specific factors related to viral infection may also play a role. These include dehydration, fever, nutritional deficiencies, and over-the-counter medications

(aspirin type) [29]. Whether in fact these factors influence the later expression of the illness is unknown and challenging to definitively verify.

Feasibility of the hypothesis

The possibility of viral linked infection in schizophrenia could assist in comprehending several phenotypic expressions of the illness. For example, it could explain the observed monozygotic discordance rates for schizophrenia since a teratogenic virus, in contrast to an environmental toxin, would not necessarily be expected to infect both twins identically. Moreover, it would be the immune response that would determine disease expression and even monozygotic twins have divergent T cell response [1]. Since HLA expression formulates during the second trimester, it is possible that viral infection at this stage of pregnancy predisposes individuals with specific HLA groups (as noted in schizophrenia) to develop an atypical immune response at this critical stage of neurodevelopment. Viral infection may also explain abnormalities of cerebral lateralization noted in schizophrenia [30,31]. This process may transpose via localized viral entry on one side of the brain [31,32]. In addition, altered immune response known to be present in cases of abnormal brain asymmetry may predispose to viral infection and its effects [31]. The delayed onset of schizophrenia from the time of birth may also be explained by viral models (e.g., lymphocytic choriomeningitis virus infection) [1].

Gene-environment interactions

Models suggest the intersection between neurodevelopmental and viral etiologies of the illness [1]. Reflecting the complexity of the gene-environment interaction, no individual viral factor could account for schizophrenia; however, susceptibility to environmental factors themselves may be under genetic control [34]. If so, then prenatal infection with some viral entity, be it influenza or some other pathogen, made possible due to some genetic facilitation or vulnerability, may increase the system's vulnerability to develop schizophrenia in adulthood [35] by affecting the critical maturational pathways required for normal brain structure and function (implicated in the pathophysiology and symptomatology of the illness). It thus may require a combination of genetic susceptibility, type or types of viral infection, timing of infection, and precise central nervous system location of infection.

Future research

There remains an imperative need to reappraise findings suggesting the role of prenatal viral infection in the pathophysiology of schizophrenia and combine them with technological advances in research method. Few areas in medicine are developing at as rapid a pace of neuropsychiatric research, answering critical questions in the field that hitherto have been inaccessible. The role of *in utero* viral infection is a perfect example of how once debunked theories in medicine may now be revisited with contemporary scientific developments. The future is now, and it behooves those in the discipline to recognize the opportunity, to ride the wave and make sense of mental illness at the biological level. The mentally ill of the world deserve no less.

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Correspondence: Dr. R.D. Strous, Beer Yaakov Mental Health Center, P.O. Box 1, Beer Yaakov 70350, Israel.
Phone: (972-8) 925-8258
Fax: (972-8) 925-8383
email: rael@post.tau.ac.il

Capsule

Reversible male immunocontraceptive

Although reliable birth control methods for females have been around for decades, the choices available for men are few. O'Rand et al. report a method of non-human primate contraception that is based on the immune response to an epididymal protein, Eppin. This non-hormonal method is effective in

monkeys that show high anti-Eppin titer, and the majority of animals that showed successful contraception were able to revert back to normal fertility.

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E. Israeli

