Medical Hypotheses 74 (2010) 555–563

Contents lists available at ScienceDirect

Medical Hypotheses

journal homepage: www.elsevier.com/locate/mehy

A unifying hypothesis of schizophrenia: Abnormal immune system development may help explain roles of prenatal hazards, post-pubertal onset, stress, genes, climate, infections, and brain dysfunction

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ARTICLE INFO

Article history:
Received 13 September 2009
Accepted 20 September 2009

SUMMARY

We propose a unifying hypothesis of schizophrenia to help reconcile findings from many different disciplines. This hypothesis proposes that schizophrenia often involves pre- or perinatal exposure to adverse factors that produce a latent immune vulnerability. When this vulnerability is manifested, beginning around puberty with changes in immune function and involution of the thymus, individuals become more susceptible to infections and immune dysfunctions that contribute to schizophrenia. Our hypothesis suggests theoretical bridges between different lines of evidence on schizophrenia and offers explanations for many puzzling findings about schizophrenia. For example, the hypothesis helps account for why schizophrenia patients tend to have had increased exposure to neurotropic infections, but most individuals with such exposure do not develop schizophrenia, and why prenatal hardships increase risk for schizophrenia, but the onset of symptoms typically does not occur until after puberty. The hypothesis also explains another paradox: lower socioeconomic status and poor prenatal care increase risk for schizophrenia at the same geographic site, but international comparisons indicate that countries with higher per capita incomes and better prenatal care actually tend to have *higher* schizophrenia prevalences. As the hypothesis predicts, (1) prenatal adversity, which increases risk for schizophrenia, also impairs post-pubertal immune competence, (2) schizophrenia patients experience elevated morbidity from infectious and auto-immune diseases, (3) genetic and environmental risk factors for schizophrenia increase vulnerability to these diseases, (4) factors that exacerbate schizophrenic symptoms also tend to impair immune function, (5) many anti-psychotic medications combat infection, (6) effects of early infections may not appear until after puberty, when they can produce neurologic and psychiatric symptoms, and (7) immune dysfunctions, such as imbalances of pro- and anti-inflammatory cytokines, may contribute to the onset of psychotic symptoms and the progressive loss of brain tissue in schizophrenia. The disruptive effects of prenatal adversity on the development of the immune system may often combine with adverse effects on prenatal brain development to produce schizophrenia. This paper focuses on the adverse immune system effects, because effects on the brain have been extensively discussed in neurodevelopmental theories of schizophrenia. We propose new tests of scientific predictions. We also point out potential clinical implications of the hypothesis; for example, individuals with schizophrenia may often have underlying infections or immune dysfunctions, such as imbalances in inflammatory cytokines, that contribute to the illness. This possibility could be tested experimentally – e.g., by clinical trials in which patients' exposure to infection is reduced or immune function is normalized.

Introduction

We propose a unifying hypothesis to help account for many puzzling and seemingly unrelated, sometimes even contradictory, sets of findings about schizophrenia. We describe how the hypothesis may help explain these findings and why they may complement, rather than contradict, one another. We describe several predictions of the hypothesis and consider empirical evidence pertinent to respective predictions. The hypothesis proposes that

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doi:10.1016/j.mehy.2009.09.040

schizophrenia often involves abnormalities in development and function of the immune system, which result from exposure to adverse factors during vulnerable periods of pre- or perinatal development.

One of the most widely reported research findings on schizophrenia is that risk for the disorder is significantly increased by pre- and perinatal exposure to a number of adverse environmental factors. These adverse factors include certain infections [1,2], maternal stress [3–5], malnutrition [6,7], and maternal medical complications [8,9]. A second finding is that the onset of schizophrenia typically does not occur until long after birth, following puberty, usually in late adolescence or early adulthood [10]. Third, increased risk for schizophrenia is significantly associated with being a male [11], and with certain environmental variables such as living in an urban setting [12] or at a higher latitude [12,13]. Fourth, many lines of evidence, including twin, family, and adoption studies, indicate that familial and genetic factors are etiologically significant in schizophrenia [14–16]. Fifth, a number of studies indicate that individuals with schizophrenia are more likely than control populations to have had exposure to a number of neurotropic infectious agents [17], but most people with this exposure do not develop schizophrenia. Finally, several lines of research suggest that certain immunologic abnormalities are more common in schizophrenia and contribute to psychotic symptoms in schizophrenia (e.g. [18].

It has been unclear how to explain and reconcile these several sets of findings in schizophrenia. The evidence that prenatal exposure to various environmental hazards increases risk for schizophrenia makes the disorder's typical post-pubertal onset puzzling, because it raises the question of why there is such a long delay between the time of prenatal insults and the first episode of the illness. This evidence for prenatal risk factors is also puzzling in view of epidemiologic data on geographic variation in the prevalence of schizophrenia [12,13,19]. Because prenatal hazards are usually associated with increased risk for schizophrenia within the same country, one might expect the prevalence of schizophrenia to be highest in developing countries, where the levels of prenatal nutrition and care tend to be the worst. In fact, schizophrenia prevalence tends to be *lowest* in developing countries, and highest in industrialized countries, including some Scandinavian countries that have low infant mortality rates and unusually good pre- and perinatal health care. Finally, it has been unclear how evidence for increased exposure to certain infections in schizophrenia patients is related to the other findings, or why such exposure might lead to schizophrenia in some individuals but not in others.

A hypothesis to reconcile different findings on schizophrenia

A unifying hypothesis to reconcile these different findings is suggested by the results of a prospective longitudinal study by Moore et al. [20,21] in the African nation of The Republic of Gambia, which has long suffered from seasonal periods of widespread food shortage and malnutrition. Moore and her colleagues found that individuals from an index cohort born during the rainy season (known there as the "hungry" season, because it is when food becomes scarce) were more than 10 times as likely to die prematurely as were individuals born during the dry season. However, the respective mortality rates for cohorts born during the rainy vs. dry seasons did not begin to diverge until after individuals were aged roughly 15 years. The excess mortality among those who have been born during the rainy season was mainly due to infectious diseases.

To explain these findings, Moore et al. [20,21] invoked the concept of prenatal programming of developing tissues, including the immune system. This concept was originally proposed by Barker [22,23] in his Fetal Origins Hypothesis. Barker's hypothesis states that undernourishment during critical periods of gestation permanently alters the function and structure of organs, but that the effects of this may not be apparent for years, or even decades, after birth [24]. Moore et al. noted that many components of the immune system begin to develop early in fetal life and continue to develop during gestation.

Moore et al. proposed that the delayed effect of prenatal malnutrition on mortality might be the result of the thymus gland protecting the index cohort from the effects of a latent vulnerability in the immune system, a vulnerability that only became manifest after the involution of the thymus gland that begins around the time of puberty. As Moore et al. pointed out, beginning at puberty parts of the thymus gland undergo a major reduction in volume. Investigations by Steinmann et al. [25] found that the volumes of the various thymic tissue components begin to decrease significantly after age 15 and continue to decrease over the next two decades. This is consistent with the idea that a latent defect in the immune system is masked until thymic involution begins, after which there is increased vulnerability to infections and immune dysfunction.

In this paper, we examine the hypothesis that an analogous mechanism plays a role in schizophrenia. The hypothesis proposes that exposure to adverse environments during vulnerable periods of gestation can disrupt the normal prenatal programming of the immune system. This creates a latent vulnerability in the individual's immune system that renders the individual more vulnerable to infectious diseases and/or dysregulation of immune processes that affect the central nervous system. The latent vulnerability in the immune system does not typically become manifest, however, until puberty, when major changes in the immune system begin to occur, and parts of the thymus gland begin to undergo a major reduction in volume. When this immune vulnerability is manifested, individuals become more susceptible to infectious and/or immune diseases that can contribute to the onset of schizophrenia.

This phenomenon would help explain why the onset of schizophrenia typically does not begin until after puberty, and why the onset of most cases occurs between puberty and age 35 – the period during which the volume of key thymic structures declines to about 20% of pre-pubescent volume [25]. This increased vulnerability to infectious or immune diseases may also help explain other findings on schizophrenia. For example, as we will discuss later, several important genetic and environmental factors that increase risk for schizophrenia are also associated with increased vulnerability to infections and/or auto-immune disorders.

Adverse pre- and perinatal environmental and genetic factors that disrupt programming of the immune system are often likely to disrupt the programming of the brain as well. We hypothesize that schizophrenia often results from the confluence of these adverse effects on both nervous and immune systems. However, the disruptive effects of prenatal hazards on central nervous system development in schizophrenia have been extensively discussed in previous research and in neurodevelopmental hypotheses of the disorder [26–29]. We therefore focus in this paper on how abnormal development and function of the immune system may help explain diverse and puzzling findings on schizophrenia, particularly ones not addressed by previous neurodevelopmental theories.

Predictions of the hypothesis and pertinent evidence

The hypothesis makes a number of testable predictions for which pertinent evidence is available.

Prediction #1: Prenatal adversity can adversely affect post-pubertal immunocompetence and thymic structure

Complementary lines of research indicate that prenatal exposure to maternal psychosocial stress and malnutrition can have