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**Prenatal and Early Life Risk Factors of Schizophrenia**

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Childhood-onset schizophrenia is an exceedingly rare mental illness whose complex, multifaceted behavioral presentation can disrupt child development and raise diagnostic and treatment difficulties for attending clinicians. The disorder, affecting one in 30,000 children, shares the same diagnostic criteria and symptoms as its adult counterpart, including delusions, hallucinations, and disorganized behavior. However, with symptoms appearing prior to the age of 13, there are important differences between early-onset and late-onset schizophrenia, where "the former may be characterized by poor premorbid adjustment, a predominance of insidious versus acute onset, and poor prognosis" (Eggers, Bunk, & Krause, 2000, p. 9; Asarnow & Thompson, 1994).

Accurate identification of the disorder is impeded by the early developmental stages of children, who are often unable to describe the disorders� complex internal experiences, as well as by clinical difficulty in distinguishing psychotic processes from normal childhood experiences (Russell, 1994). Further complicating accurate diagnosis is differentiation of the presenting symptoms from other, more common childhood difficulties. Regrettably, children with early onset schizophrenia are often misdiagnosed and treated for myriad other disorders, leaving the underlying illness unidentified and contributing to the deterioration of health (Schaeffer & Ross, 2002). This reality impels researchers to understand what causes schizophrenia. As recently stated by Gilmore (2010),

The short answer may be "nothing" or more precisely "no one thing." In most cases, schizophrenia is an end result of a complex interaction between thousands of genes and multiple environmental risk factors—none of which on their own causes schizophrenia. (p. 9)

The role of genetics in the development of schizophrenia was first recognized in 1916 by Rudin, who documented clustering of this disorder in families. Data indicate that a child whose first-degree relatives have a history of schizophrenia has a 10% chance of developing the disorder, as compared to a 1% chance among the general population (National Institute of Mental Health [NIMH], 2009). The risk remains elevated even if the child is adopted and raised by parents with no history of the disorder (Shih, Belmonte, & Zandi, 2004). Moreover, nearly all twin studies show that monozygotic twins (MZ) are at an increased risk for developing the disorder, as compared with their dizygotic (DZ) counterparts (Shih et al., 2004; Cardno et al., 1999).

However, family history is only a part of the equation when it comes to childhood schizophrenia. Environmental stressors have been shown to increase the risk of developing schizophrenia, even in individuals with a confirmed genetic predisposition. Childhood-onset schizophrenia may be especially influenced by "a combination of factors which in some cases leads to clinically recognizable symptoms at an unusually young age" (Kallman & Roth, 1956, as cited in Nicolson & Rapoport, 1999). Questions about prenatal and early developmental experiences contributing to pathological alterations in brain structure are evolving among the clinical and research community (Bale et al., 2010). In this article, we critically review the recent literature examining the contribution of environmental and prenatal factors to the development of schizophrenia. These factors include (a) maternal stress response, (b) maternal infection, and (c) prenatal nutrition.

**Maternal Stress Response**

The relationship between maternal stress and negative fetal outcomes has been well established (Mulder et al., 2002; Weinstock, 2005; Kofman, 2002). Studies show that maternal stress results in reduced blood flow to the uterus, transplacental transport of maternal stress hormones, and secretion of placental corticotrophin-releasing hormone to the fetus (Mulder et al., 2002). These processes result in a wide range of outcomes, ranging from spontaneous abortion, preterm delivery, and reduced birth weight to fetal growth restriction, structural brain malformations, and growth inhibition of the developing nervous system (Mulder et al., 2002). The frontal cortex and hippocampus, which are the two brain structures shown to be particularly affected by prenatal stress in animal studies, have important implications for memory, emotional regulation, response inhibition, and spatial navigation. These are common executive functions, which require extensive processing resources, that are impaired in children with schizophrenia (Asarnow et al., 1994).

Recent studies have concentrated on prenatal/maternal exposure to severe adverse life events, including acts of terrorism, natural disasters, and bereavement. According to an investigation of acute maternal stress, children who suffered in utero first trimester exposure to the Arab–Israeli war demonstrated an increased incidence for developing schizophrenia. Similar findings have been reported by researchers studying mothers exposed to the stress resulting from the death or illness of a relative (Khashan et al., 2008). In a cohort of 1.38 million people, researchers found that children whose mothers were exposed to the death of a relative during the first trimester were 1.67 times more likely to develop schizophrenia and related disorders (Khashan et al., 2008).

**Maternal Infection**

A commonly noted complication of pregnancy, producing deleterious effects on the developing fetus, is infection. Agents such as rubella, herpes simplex virus, cytomegalovirus, and toxoplasmosis disrupt neurodevelopment and lead to fetal brain abnormalities, including intellectual disabilities, cerebral palsy, and hearing and vision loss (Brown & Derkits, 2010; Brown, Cohen, Greenwald, & Susser, 2000; Brown & Susser, 1996; Simon, 2007). When infected, the body�s natural immune response is to generate pro-inflammatory cytokines that identify and destroy viral and bacterial agents (Harvard Medical School, 2009). Much like the body�s response to stress, these particular substances change the central nervous system response to injury and infection by "altering neuronal survival and differentiation as well as dendrite growth and complexity" (Meyer et al., 2006, p. 4752).

Although known as the regulators of healthy brain development, pro-inflammatory cytokines can also influence brain function and later behavioral development (Meyer et al., 2006; Meyer, Feldon, & Yee, 2009; Smith, Li, Garbett, Mirnics, & Patterson, 2007). Long-lasting behavior changes consistent with symptoms of schizophrenia have been documented, including inhibition of startle response, deficits in the ability to ignore irrelevant information, and disruption in social interaction (Shih, Tu, & Patterson, 2005). Studies also show that animal offspring exposed to prenatal maternal infection have structural brain abnormalities frequently noted in brains of persons diagnosed with schizophrenia. These abnormalities include reduced total brain and cortical gray matter volumes, ventricular enlargement, and regional decreases in frontal cortex and temporal–limbic structures (Short et al., 2010).

Several epidemiological studies concentrated on the relationship between prenatal exposure to influenza and subsequent development of schizophrenia (Brown, 2006; Brown & Derkits, 2010; Brown, Cohen, Greenwald, & Susser, 2000; Machon et al., 2002; Mednick, Huttunen, & Machon, 1994). Greater incidence of schizophrenia was first noted among Finnish individuals who were exposed to the 1957 influenza epidemic during their second trimester of gestation (Mednick et al., 1994). Later investigations moved beyond isolated epidemiological events and focused on links between clinically documented infection and schizophrenia. Using serological evidence of maternal exposure to influenza, researchers demonstrated that exposure to the virus from "approximately the midpoint of the first trimester to the midpoint of the second trimester increased the risk of schizophrenia by a factor of 3" (Brown et al., 2004, p. 778).

Adding to the infection hypothesis are studies examining the connection between inflammatory mediators and psychosis. Researchers studying children and adolescents diagnosed with psychotic disorders found evidence of elevated serum concentrations of S100b, a protein implicated in various functional processes, in blood samples (Falcone, Carlton, Franco, & Janigro, 2009). Elevations of this protein are believed to serve as a biomarker of blood-brain barrier disruption, which normally restricts the passage of harmful substances to the brain. It is suspected that, when the function of the blood–brain barrier is disrupted, the resulting neuroinflammation and neuro-degeneration leads to psychiatric disease.

**Prenatal Nutrition**

Prenatal malnutrition is one of the bestdocumented environmental factors playing a significant role in fetal development. Often quoted are the studies based on the Dutch Hunger Winter of 1944, a famine in western Holland resulting from the Nazi blockade (Hulshoff et al., 2000). Children exposed to this devastating event during the first trimester of gestation were found to have increased incidence of clinical brain abnormalities associated with schizophrenia. These included decreased intracranial volume and focal white matter hyperintensities, indicating injury to the neuronal axons and the resulting loss of intracranial blood flow (Hulshoff et al., 2000; UC Davis Medicine, 2007). Applying this knowledge to animal studies, researchers demonstrated that "causing a defect in white matter is sufficient to cause biochemical and behavioral changes resembling those seen in neuropsychiatric disorders" (Children�s Hospital Boston, 2007). White matter pathology was found to impair the brain�s ability to store and manipulate information, as it damages the frontal lobes of the brain (UC Davis Medicine, 2007).

**Limitations**

According to the growing body of research, schizophrenia is conceptualized as a neurodevelopmental disorder resulting from the interaction of genetics and early environmental risk factors, with an earlier onset of illness connected to stronger genetic and environmental influences (Nicolson & Rapoport, 1999). However, the pathophysiological mechanisms that underlie the associations between genetics, prenatal risk factors, and the development of childhood schizophrenia have yet to be established.

Given the rarity of childhood-onset schizophrenia, whose prevalence is suggested to be about 0.01–0.05/1000 (Eggers et al., 2000), and its fairly recent introduction in research literature, our knowledge of the disorder is limited by the small number of cases analyzed. The issue is further complicated by the diagnostic confusion surrounding the disorder, as attempts to distinguish symptoms of psychosis from common developmental experiences of childhood as well as other psychiatric disorders continue to pose a challenge to many clinicians (Gonthier & Lyon, 2004; Khurana, Aminzadeh, Bostic, & Pataki, 2007). Although several prenatal factors have been identified, none of these factors indicate a causal relationship in the development of schizophrenia. At the same time, however, "because a given risk factor may be associated with several adverse health outcomes, these findings do not preclude the existence of a causal relationship between perinatal risk factors and schizophrenia" (Verdoux, 2004, p. 162).

Another limitation pervading literature on the environmental causes of schizophrenia is the interconnectedness and the resulting confounding of the risk factors studied as well as contribution of these factors to a broad range of psychiatric disorders (Verdoux, 2004). For example, a mother who experiences stress while pregnant can easily acquire an infection as a result. A pregnant mother suffering from malnutrition is also likely to be exposed to stressful or even traumatic events at the same time. Her offspring will have an increased risk of developing a wide range of mental health problems. The lack of specificity of most of the risk factors discussed not only makes it difficult to determine their influence and contribution in the etiology of schizophrenia, but also underscores the complexity of the issue. It is clear that continued scientific exploration is needed to elucidate the environmental etiology of schizophrenia as well as its interplay with genetic predispositions.

**Implications for School Psychologists**

Childhood-onset schizophrenia is a complex, multifaceted disorder whose early presentation can include social skill deficits, developmental delays, significant academic difficulties, learning disabilities, and persistent behavioral problems. Children will typically first present with nonspecific yet concerning behaviors, which gradually progress into full-fledged symptoms. The relative rarity of childhood-onset schizophrenia often leaves clinicians and educators unsure about how to recognize and meet the needs of affected students. Children affected by this disorder can be reasonably expected to exhibit "a rather pervasive set of cognitive, social, educational, and adaptive skill deficits" (Gonthier & Lyon, 2004). These deficits may include the following (adapted from Children�s Hospital Boston):

* Difficulty telling dreams from reality (distorted perception of reality)
* Confusing television with reality (confused thinking)
* Illogical thinking, loose associations, and impaired conversational skills (language and communication deficits)
* Difficultly forming and engaging in typical peer relationships (social difficulties)
* Appearing unresponsive in facial features or body language and displaying inappropriate emotional responses, such as laughing at a sad event
* Hearing voices or seeing irrational images, such as monsters, ghosts, or animals (hallucinations)
* Displaying excessive fear, suspiciousness, or paranoia regarding day-to-day concerns (delusions)
* Difficulty maintaining attention or concentrated thought
* Decline in self-care skills and physical complaints, including changes in sleeping patterns or appetite
* Disorganized or catatonic behavior, such as repeating rhythmic gestures or motor movements or sitting and staring, as if immobilized, for prolonged periods
* Deteriorating cognitive functioning, particularly high-order thinking skills including information processing, the retention of learned information and abilities, and the ability to acquire new information and skills

These clinical symptoms can be easily diagnosed as other common childhood disorders (Khurana et al., 2007). In fact, one common theme among families of children eventually diagnosed with schizophrenia is the "lack of a clear and finite diagnosis at an earlier stage of development" (Schaeffer & Ross, 2004, p. 543). Despite parents� insistence that something was "seriously wrong" with their child, there was an "average 2-year delay between the onset of symptoms and the diagnosis of schizophrenia with related antipsychotic medication administration, well beyond the 6-month window generally considered as early diagnosis and treatment in adolescent schizophrenia" (Schaeffer & Ross, 2002, p. 543). Some of the more common misdiagnoses include the relatively frequent childhood disorders, such as pervasive developmental disorder (i.e., autism), attention deficit hyperactivity disorder, major depressive disorder, bipolar disorder, oppositional defiant disorder, and emotional disturbance (Schaeffer & Ross, 2002).

Although treatment and management of childhood-onset schizophrenia does not fall within the required scope of competencies of most school psychologists, we must be able to recognize the symptoms, make appropriate referrals, and coordinate educational services for the affected children. In order to properly differentiate the disorder�s earliest warning signs from the more frequent childhood problems, school psychologists must be especially observant of children who exhibit a constellation of symptoms approximating a common childhood disorder, in addition to atypical behaviors that do not seem to fit with it. This includes paying attention to the context(s) in which symptoms emerge, assessing the developmental appropriateness of presenting behaviors, and considering family, prenatal, and environmental factors during the initial evaluation process. Appropriate identification of the disorder will result in not only an appropriate psychiatric referral but also in effective treatment and educational services.

Often, children with schizophrenia will qualify for services under the IDEA category of "emotionally disturbed" (Gonthier & Lyon, 2004). Services may include a small class size, social skills training, speech/language therapy, and physical or occupational therapy. A specialized behavior plan may also be needed to address common behavior issues including inattention, aggression, and defiance. Sensitive and thorough initial assessment is likely to translate into meaningful involvement with the child and her/his family, facilitating parent– school collaboration necessary to ensure the best possible long-term outcome for the child. Ultimately, this is what defines our role as school psychologists.

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