The Neurodevelopmental Model of Schizophrenia: What Can Very Early Onset Cases Tell Us?

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Neurodevelopmental models of schizophrenia that identify longitudinal precursors of illness have been of great heuristic importance, focusing mostly on etiologic research during the past two decades. These models have varied considerably with respect to specificity and timing of hypothesized genetic and environmental "hits," but have largely focused on insults to prenatal brain development. The study of early onset cases of schizophrenia is important as any model must also account for the wide range of age of onset and stratification by age of onset has been fruitful for genetic understanding of illness [1].

In recent years, longitudinal brain imaging studies of healthy children indicate that progressive brain changes are more dynamic than previously thought, [2] with gray matter volume loss particularly striking in adolescence [3]. Patients with very early onset schizophrenia show a similar developmental pattern, but it is more exaggerated [4]. This supports an extended period of abnormal neurodevelopment in schizophrenia in addition to (theory at least secondary) an earlier "lesion."

In schizophrenia, many subtle cognitive, motor, and behavioral deviations are seen years before illness onset [5]. Studies of early onset schizophrenia indicate more striking premorbid neurodevelopmental impairment suggesting a more malignant process across a broad developmental period [6,7]. More recent studies suggest that there is an increased rate of brief "positive"(hallucinations and/or delusions) symptoms in childhood in those who become schizophrenic as adults, indicating more widespread earlier abnormality in brain function than was thought previously and greater continuity regarding psychosis per se than has been thought previously [R.PR07-2-IC-01.15].

Family studies of very early onset cases indicate higher rates of schizophrenia and/or spectrum disorders [9,10]. In addition, schizophrenia susceptibility genes and chromosomal abnormalities, particularly as examined for early onset populations (GAD1, 22q11DS), are associated with more severe premorbid neurodevelopmental abnormalities [11]. Several candidate genes for schizophrenia (dysbindin) are more generally associated with lower cognitive abilities in schizophrenic and other pediatric populations [12]. Postmortem human brain and developmental animal studies document multiple and diverse effects of developmental genes (including schizophrenia susceptibility genes), at sequential stages of brain development [13]. These may underlie the broad array of premorbid cognitive and behavioral abnormalities seen in schizophrenia, and cognitive development more generally. Clearly, as gene expression varies by developmental period, genetic effects often will be manifest later in development as documented by adoption studies of cognitive development [14]. Therefore, there are compelling genetic mechanisms to account for progressive developmental abnormalities seen in schizophrenia.

Obstetrical risk studies have not been stressed here because they have not been found to be increased in early onset populations [10]. However, here too, increased specificity for the most relevant environmental risk factors such as exposure to prenatal infection, and their interaction with susceptibility genes and/or action through phase specific altered gene expression [15] now strengthen and modify the neurodevelopmental theory of schizophrenia.

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