Editorial: Research Progress in Early-Onset Schizophrenia

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A substantial proportion of patients with schizophrenia experience the onset of their illness by age 18. Data from phenomenological, cognitive, neuroimaging, and genetic studies suggest a similar profile of clinical and neurobiological abnormalities between early- and adult-onset patients. However, children and adolescents with schizophrenia have been found to have more severe premorbid neurodevelopmental abnormalities, worse long-term outcome, more cytogenetic anomalies, and potentially greater loading of family histories for schizophrenia and associated spectrum disorders than their adult counterparts. Together, these data support a hypothesis that early-onset schizophrenia may reflect a more severe form of the disorder associated with a greater genetic predisposition. It is anticipated that future imaging and genetic studies of this cohort will provide further insight into the neurodevelopmental origins of schizophrenia and the complexity by which genetic and environmental factors interact to modulate susceptibility and/or disease phenotype. The articles on this theme provide updated findings from brain magnetic resonance imaging, neurocognition, and clinical trials in this unique cohort.

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Across various branches of medicine, the study of patients with an early age of onset of disease has been a valuable approach toward understanding phenotypic patterns and pathogenic mechanisms of disease because they will have a lesser exposure to possibly relevant (and confounding) life events. This special section of Schizophrenia Bulletin marks the second themed issue of this journal concentrating on early-onset schizophrenia (EOS; onset of psychotic symptoms by age 18) which appears to represent a severe, more familial variant of typical schizophrenia.1 The first issue, published in 1994 and edited by Robert and Joan Asarnow,2 provided strong evidence that the syndrome of childhood-onset schizophrenia existed and described the phenomenological similarities between patients with childhood- and later-onset schizophrenia. At that time, neurobiological models of schizophrenia largely focused on “early” neurodevelopmental disturbances contributing to the etiology and pathophysiology of schizophrenia. However, this formulation failed to explain many key aspects of schizophrenia including the wide range of age at onset; the nature of perceptual disturbances; and why some children in the general population have these anomalous experiences but remain well, while a minority progress to the full clinical syndrome.3 Over the past 13 years, the study of children and adolescents with schizophrenia has highlighted the possible role of “late” (ie, adolescent period) neurodevelopmental changes occurring soon after the onset of psychosis which may involve an acceleration of normal brain maturational processes. The 6 articles selected for inclusion in this issue provide a representative, though clearly not exhaustive, demonstration of some of the critical progress made in the study of EOS.

Adolescence represents a critical period for maturational processes such as synaptic pruning and myelination in the prefrontal cortex which is paralleled by increased abilities in abstract reasoning, attentional shifting, response inhibition and processing speed, and a decrease in neurologic soft signs in typical development. In this issue, 3 different groups (National Institute of Mental Health [NIMH], University of Minnesota,4 Harvard University) have applied magnetic resonance imaging techniques to increase our understanding of the aberrant neurodevelopmental processes in schizophrenia. Studies conducted at the NIMH from a unique cohort of treatment-refractory patients with EOS who received prospective anatomic brain magnetic resonance imaging scans at 2-year intervals post-onset of psychosis have found that cortical gray matter (GM) loss is marked and progressive in patients during adolescence and becomes more circumscribed by early adulthood. Second, using diffusion tensor imaging, White and colleagues review cross-sectional data demonstrating abnormalities in white matter microstructure in corticolimbic regions (eg, anterior cingulate and hippocampus) in adolescents with schizophrenia.5 Together, these data suggest that there may be an extended...
time period of abnormal neurodevelopment in schizophrenia and provide support for a hypothesis that primary cortical pathology could possibly lead to dysregulated limbic system function in adolescents with schizophrenia. This model is potentially consistent with emerging data from studies of prodromal subjects which have shown rapid GM loss in prefrontal areas in those who convert to psychosis and earlier structural imaging studies in adolescents with schizophrenia which found little hippocampal volumetric pathology early in the course of schizophrenia in adolescents. In keeping with emerging data from the adult literature suggesting that psychosis is an important dimension characterizing both schizophrenia and bipolar disorder, Frazier and colleagues have applied structural magnetic resonance imaging to clarify whether there are distinct neurobiological abnormalities separating these 2 disorders in pediatric populations.

Cognitive impairment is a prominent and debilitating feature of EOS. In comparison to adults, children and adolescents with schizophrenia often present with higher rates of subtle cognitive, motor, and behavioral deviations which are seen years before the onset of psychotic symptoms. There is some evidence that schizophrenia susceptibility genes and chromosomal abnormalities associated with EOS may contribute to some of the premorbid neurodevelopmental abnormalities (ie, GAD1, 22q11DS) and widespread generalized cognitive deficits (ie, dysbindin) characteristic of the disorder. Longitudinal family studies “genetic high-risk” designs of unaffected children provide a framework for understanding the developmental progression of symptoms and the mechanisms by which environmental/genetic risk factors affect brain circuitry and trigger the onset of psychosis. In this issue, Ross and colleagues demonstrate the stability of cognitive deficits in working memory and behavioral inhibition in 25 school-age children with a schizophrenic parent over 2 time points about 2 years apart. Also in this issue, Frangou and colleagues present data demonstrating the stability of cognitive deficits in adolescents with schizophrenia post-onset of psychosis. Together, these data demonstrate that cognitive deficits represent a core feature of schizophrenia that are present before the onset of clinical symptoms, remain relatively stable across clinical state despite the administration of antipsychotic treatment in patients, and are seen in unaffected first-degree relatives.

This special section concludes by addressing pharmacotherapy. Although the adult literature suggested that an early-onset of schizophrenia was associated with a poor response to neuroleptic treatment and worse long-term outcome, until quite recently empirical research on the pharmacological treatment of this population was sparse. Three recent industry-sponsored studies have now demonstrated the efficacy of second-generation antipsychotics (risperidone, olanzapine, and aripiprazole) relative to placebo in adolescents with schizophrenia (see review by Kumra and colleagues in this issue). However, overall clinical response was disappointing in that a substantial proportion of subjects who received active treatment in these short-term studies were left with significant levels of negative symptoms which is a predictor of poor long-term functional outcome. In this regard, the utility of a clozapine trial for treatment-refractory youth with schizophrenia has now been well established in 3 separate controlled studies. An overarching theme across all these treatment studies has been that youth appear more susceptible to antipsychotic-induced weight gain, as well as adverse metabolic side effects associated with second-generation antipsychotics which could have severe long-term consequences. To date, there have been few head-to-head comparisons of the second-generation antipsychotic agents, and thus it remains unclear whether the “newer” drugs with theoretically better side effect profiles (eg, quetiapine, aripiprazole, and ziprasidone) are equally effective to standard drugs which have been available for longer periods of time and which are more widely used in the treatment of EOS (eg, risperidone). As noted in this review, there is a dearth of research on adjunctive psychosocial treatments in EOS to enhance medication adherence, processing speed, and social cognition.

In summary, considerable progress has been made over the past decade toward understanding the pathophysiology and therapeutic management of child- and adolescent-onset schizophrenia. To date, most of the developmental precursors for schizophrenia identified thus far are nonspecific. Thus, it is likely that preventative efforts aimed at the disorder as it more typically presents, in late adolescence or early adulthood, would have to be initiated during adolescence when early markers/clinical symptoms heralding the onset of psychosis first appear reliably. In this regard, the study of EOS cases should continue to provide important insights into the impact of various risk factors associated with schizophrenia on trajectories of brain development and the effects of intervention. The major challenges in undertaking research in this cohort with regards to recruiting an informative sample of patients will likely be remedied by undertaking collaborative, multisite studies. This could be accomplished by leveraging existing infrastructure and tools from ongoing adult schizophrenia studies (eg, Mental Illness and Neuroscience Discovery Institute consortium) by adding pediatric subjects.

References


