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Early-Onset Psychosis and Child and Adolescent Schizophrenia

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"Our lives disconnect and reconnect, we move on, and later we may again touch one another, again bounce away. This is the felt shape of a human life, neither simply linear nor wholly disjunctive nor endlessly bifurcating, but rather this bouncey-castle sequence of bumpings-into and tumblings-apart."
— Salman Rushdie, *The Ground Beneath Her Feet*

We are excited to introduce this special issue of SJCAPP about early-onset psychosis (EOP) and schizophrenia in children and adolescents. Several years ago, an editorial in *Nature* described schizophrenia as "the worst disease affecting mankind" (1). We know that approximately 1% of the world's population is directly affected by this debilitating psychiatric disorder at some point during their lives (2). Every year, more than 5,000 new articles about schizophrenia spectrum disorders and psychosis are added to PubMed (3). Schizophrenia remains one of the most mysterious and severe mental disorders. It has a complex and heterogenic symptomatology that causes enormous suffering to patients and their relatives, and it is generally considered a costly burden on society, although its true financial cost is somewhat difficult to estimate (4,5). In the *Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition* (DSM-5), schizophrenia is defined as: "…a disorder that lasts for at least 6 months and includes at least one month of active-phase symptoms (i.e., two [or more] of the following: delusions, hallucinations, disorganized speech, grossly disorganized or catatonic behavior, negative symptoms)" (6). The DSM-5 further states that "no single symptom is pathognomonic of schizophrenia" (6). Across different diagnostic systems, there seems to exist a general understanding that schizophrenia is a heterogeneous syndrome composed of various symptoms with different pathogeneses and etiologies. However, there is also consensus that the phenotypic characteristics include positive symptoms (e.g., hallucinations, delusional thoughts), negative symptoms (e.g., apathy, lack of emotions, poor or absent social functioning), bizarre behavior, and a range of cognitive dysfunctions, including disorganized thoughts, difficulty concentrating and completing tasks, reduced memory, and deficits in the processing of information. These symptoms have been found in cross-cultural studies conducted by the World Health Organization since the International Pilot Study in Schizophrenia was initiated during the 1960s; this study proved that schizophrenia and its related symptomatology are found worldwide, although the course and outcomes of the illness may vary (7).

Schizophrenia affects more than just mental health. Patients who are diagnosed with schizophrenia die 12 to 15 years earlier than the average population (8), and current studies have indicated that the mortality difference continues to increase, mainly as a result of suicide. The incidence rates for schizophrenia peak around the age of 22 years (9), but one third of the individuals who will develop the disorder do so before they are 18 years old (10). Schizophrenia that appears in children and adolescents is accepted to be clinically and biologically coherent with adult-onset schizophrenia (AOS). However, there are some differences. Patients with early-onset schizophrenia (EOS) display a more severe clinical prognosis and a greater neurodegenerative trajectory, and they seem to be less responsive to treatment as compared with patients with AOS. Schizophrenia that emerges in patients before they are 18 years old is divided into two groups: 1) EOS, with an onset between the ages of 13 and 17 years and prevalence rates of 1 to 2 per 1,000 population; and 2) very EOS, which begins

before the age of 13 years and which has a prevalence that is estimated at 1 per 10,000 population (11). The modern construct of EOS differs significantly from that used during much of the twentieth century. Until the early 1970s, children who would now be diagnosed within the autism spectrum would have been diagnosed with schizophrenia, and widespread uncertainty existed regarding the validity of a schizophrenia diagnosis in children and adolescents (12). With the introduction of the DSM-III and the *International Statistical Classification of Diseases and Related Health Problems, 9th Revision,* the specific criteria that were used to define childhood and adolescent schizophrenia were removed: the same criteria have since been used to diagnose schizophrenia in children, adolescents, and adults. With the alignment of the defining criteria, prospective studies have demonstrated good validity of the diagnosis for children and adolescents; youths who are diagnosed with schizophrenia display high stability with regard to the phenotypical expression of the disorder into adulthood (13). Studies of neuropsychological functions and brain structure in people with schizophrenia have shown the same degenerative patterns, regardless of the patient's age at the onset of the disorder (14).

The discrete developmental trajectories of schizophrenia remain obscure, but recent research has enhanced our understanding of the disorder and of the underlying etiological factors (3,15,16). Gene-environment studies have emphasized genetic factors that affect an individual's vulnerability to the development of schizophrenia, and twin studies have shown that the syndrome has heritability rates of approximately 80% (17,18). There has been a substantial effort from those supporting the medical disease model to demonstrate that schizophrenia has a biological origin. This stance is supported by studies that have demonstrated a genetic predisposition for schizophrenia among family members, twins, adoptees, and offspring of twins (19). Other studies have shown that schizophrenia is associated with structural brain abnormalities (20) and with biochemical imbalances that are mostly associated with the functioning of the dopaminergic system (21).

Epidemiological studies also indicate that environmental factors affect the rate of schizophrenia (8;22-24), including adverse experiences in childhood (25). Living in urbanized communities raises the risk of schizophrenia (26), and the tendency to develop schizophrenia is higher among certain ethnic groups as compared with native-born individuals (27).

With respect to long-term prognosis, longitudinal studies that have followed patients with schizophrenia for more than 25 years have suggested that approximately 35% of patients recover fully and that another 35% function independently and are self-supporting, with some possibility of residual symptoms (28). A 25-year follow-up study that evaluated profoundly disabled patients with schizophrenia with an average of 16 years of schizophrenic symptoms and an average total disability of 10 years found that 68% of these subjects were free of schizophrenic symptoms and that 45% were free of all psychiatric symptoms at 25 years (29).

Specifically, studies of EOS show that the disease displays strong associations with poor premorbid functioning and a reduction in normative development (30), and this diminution seems to be more severe in patients with EOS as compared with AOS. In addition, studies have shown that, in about 20% of adolescents who have been diagnosed with schizophrenia, clear language and motor developmental delays are present; these delays are only found in about 10% of patients with AOS (31). Research has also reported a substantial difference in the premorbid intelligence quotients of patients with EOS as compared with those with AOS, with patients with EOS scoring roughly 10 to 15 points lower (30). Patients with EOS generally have more negative symptoms, more severely incoherent thoughts, and a more profoundly disordered sense of self, whereas AOS is associated with more severe positive symptomatology, such as paranoid delusions (32). As compared with the relatively high remission rates for patients with AOS, only 12% of patients with EOS are in full remission at discharge. In several prospective follow-up studies, patients with EOS have displayed a chronically disabling course of illness and severely impaired functioning well into adulthood (13,33).

Important EOS predictors of diminished functioning point to premorbid cognitive and social deficiencies (33), long periods of untreated psychosis, and a long first psychotic episode (34).

This special issue of SJCAPP addresses several of the issues just described, and the two included commentaries build further on these ideas. In the first commentary, Aggernæs connects the four articles included in this issue, and she describes the growing evidence of a shared genetic risk for autism, attention-deficit/hyperactivity disorder, and schizophrenia. She emphasizes the importance of the thorough assessment of the patient in addition to the need for intervention during the first psychotic episode and the prodromal phase. Nordgaard and colleagues also address this in their commentary, and they discuss the need for more specific instruments for the assessment of clinically high-risk patients. Patients who experience their first episode of psychosis need to be treated early and optimally to

decrease morbidity and to improve the outcomes of their illnesses. This is a special challenge for the treatment of children due to the associated side effects of antipsychotic drugs. The article by Haapasalo-Peru and colleagues discusses the growing trend of prescribing antipsychotics to young people and calls for the development of non-pharmacological treatment modalities, as described in a recent review (35).

These relatively new research findings related to EOS and its devastating prognosis obligate researchers to continue their explorations into the ways in which the early forms of schizophrenia and psychosis emerge, how they develop in children and adolescents, and how they carry over into adulthood.

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