The meaning of childhood attention-deficit hyperactivity symptoms in patients with a first-episode of schizophrenia-spectrum psychosis

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ABSTRACT

Objective: To examine childhood ADHD symptoms in regard to their association with a number of illness-related variables including risk factors, early neurodevelopment, premorbid functioning and clinical characteristics in patients with schizophrenia-spectrum psychoses.
Methods: One-hundred and twenty-two first-episode patients with DSM-IV schizophrenia-spectrum disorders were retrospectively assessed by means of their biological mothers for childhood ADHD symptoms. Using correlational analyses and hierarchical regression models, the severity of ADHD symptoms was examined in relation to familial liability to schizophrenia, obstetric complications, milestones attainment delay, premorbid functioning during childhood and adolescence, age at illness onset, episode psychopathology and response to treatment after one-month trial with antipsychotic medication.
Results: Twenty-one patients (17%) met DSM-IV criteria for childhood ADHD. Univariate analyses showed that severity of childhood ADHD symptoms was related to male gender, obstetric complications, delayed milestones attainment, poor school functioning and an earlier age of onset of psychotic symptoms. Hierarchical regression analyses showed that severity of childhood ADHD symptoms was independently predicted by obstetric complications and neurodevelopmental delay, with no further variables entering in the regression models. Path analyses showed that obstetric complications had both direct and indirect effects, through neurodevelopmental delay, on ADHD symptoms.
Conclusions: These findings are consistent with a neurodevelopmental model of schizophrenia and with the hypothesis of shared environmental risk factors between ADHD and schizophrenia-spectrum disorders. Childhood ADHD symptoms in schizophrenia-spectrum disorders appear to be an epiphenomenon of obstetric complications and early neurodevelopment delay with no further influence on the clinical expression of the illness.

1. Introduction

The characteristic symptoms of schizophrenia and spectrum disorders, which typically emerge in late adolescence or early adulthood, are preceded in a substantial proportion of individuals by a broad range of childhood behavioral abnormalities (Mehl, 1962; Gittelman-Klein and Klein, 1969; Fish et al., 1992; Cannon et al., 2009), which are central to a neurodevelopmental model of schizophrenia (Weinberger, 1987; Murray and Lewis, 1987). The neurodevelopmental theory of schizophrenia is relevant because it has directed

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scientific attention to the origins of the disorder in early life, many years before the illness can be diagnosed. Developmental psychopathology of schizophrenia-related disorders likely arises from the dynamic interaction between genetic and environmental factors, some specific and some non-specific. In support of this, evidence has accumulated indicating that the emergence of certain psychopathologies during childhood and adolescence including neurodevelopmental deviance, cognitive dysfunction, and a broad range of behavioural disturbances parallels age-dependent anomalies of maturation processes in the brain (Keshavan et al., 2004; Paus et al., 2008).

In recent years, an increasing focus of interest has been the study of symptoms of attention-deficit hyperactivity disorder (ADHD) during childhood in subjects with schizophrenia (Elman et al., 1998; Rubino et al., 2009) or who are at risk of developing the disorder (Niemi et al., 2003; Keshavan et al., 2002, 2008). These studies have consistently shown that a history of childhood ADHD is more frequent in patients with schizophrenia-spectrum disorders and in subjects at risk of developing these disorders than in the general population. However, the reported prevalence rate of ADHD in these conditions has varied widely, ranging between 5% (Stahlberg et al., 2004) and 84% (Ross et al., 2006). These divergent prevalence figures are likely due to differences in sample composition, assessment methodology and timing for diagnosing ADHD. For example, while high-risk studies have consistently reported that about one-fourth of at-risk subjects present with ADHD (Rieder and Nichols, 1979; Keshavan et al., 2008), cohort studies of schizophrenia patients have reported variable prevalence rates, with studies of early-onset schizophrenia reporting the highest ones (Ross et al., 2006; Karatekin et al., 2007), which likely reflects the higher developmental impairment in these patients.

Although evidence for the presence of ADHD symptoms in children at risk for, or who eventually develop schizophrenia-spectrum disorders is well established, the correlates of these symptoms with illness-related characteristics are less clear. High-risk studies have shown that, compared with subjects without ADHD, those with ADHD display more neurocognitive dysfunction (Rieder and Nichols, 1979; Öner and Munir, 2005), more functional impairment (Öner and Munir, 2005), more psychotic-like symptoms (Keshavan et al., 2002) and an increased risk for developing schizophrenia-spectrum disorders (Rieder and Nichols, 1979; Keshavan et al., 2008). Only two previous studies, which were conducted in early-onset patients, have compared schizophrenia patients with and without a history of ADHD. These studies yielded contradictory results regarding differences among groups across a number of clinical variables (Elman et al., 1998; Karatekin et al., 2007). Given that studies of both at-risk subjects and early-onset schizophrenia are problematic regarding generalizability of findings, along with the possibility that associations between ADHD symptoms and clinical features are due to other intervening variables, the meaning of childhood ADHD symptoms in patients with schizophrenia and related disorders remains largely unknown.

In this study we retrospectively examined ADHD symptoms during childhood in never-treated patients with a first-episode of schizophrenia-spectrum disorders and analyzed their unique associations with well-known risk factors for schizophrenia such as familial liability and obstetric complications (OCs), and with a number of relevant illness-related variables including early developmental impairment, premorbid adjustment during childhood and adolescence, age at illness onset, index episode psychopathology and response to treatment. Based on previous findings, we hypothesized that the prevalence of ADHD largely exceeds that reported in the general population, and that ADHD symptoms are related to familial liability to schizophrenia, poor premorbid adjustment, more severe psychopathology and poor response to treatment. Given the lack of previous data regarding the relationship of ADHD symptoms with developmental delay and age at onset of the psychotic disorder, no specific hypotheses regarding these relationships were formulated.

2. Method

2.1. Participants

This study is part of an ongoing study on antecedents, phenomenology and response to treatment of first-episode, drug-naive patients with schizophrenia-spectrum disorders. Full details of the original study design, sampling strategy and assessment methodology are available elsewhere (Peralta et al., 2010). The study population for the present study was made of 122 patients who were admitted for their first treatment and met a DSM-IV diagnosis of schizophrenia ($n=85$), schizophreniform disorder ($n=28$) or schizoaffective disorder ($n=9$). The study was approved by the local ethics committee and all patients or their legal representatives gave written informed consent to participate.

Inclusion criteria were: age 15–65 years, no previous exposition to antipsychotic drugs, and available biological mother. Exclusion criteria were: a history of drug dependence, evidence of organic brain disorder, IQ<70, or meaningful medical illness. Patients' biological mother provided information about the retrospectively collected variables, and only those patients whose mothers provided reliable information, as judged by the interviewer, were included in the study. The rationale for the exclusion criteria was to avoid potential secondary sources of neurological dysfunction, which was one of the main aims of the stem study.

The mean age of the patients was 27.8 years (s.d.=8.35); 84 were men and 38 women, and 111 were single. The average years of education was 12.2 (s.d.=3.78), and 87 patients (71%) were full or part time employed before the index admission.

2.2. Assessments

The subjects were administered the Comprehensive Assessment of Symptoms and History (CASH) (Andreasen et al., 1992), which served to assess demographics, diagnosis, illness-related variables and psychopathology. Diagnoses were made by consensus between the two senior psychiatrists (VP and MJC) at the end of the hospitalization period using all the available information.

2.2.1. Outcome variables

The primary outcome measure of interest was the 10-item parents' version of the Wender Utah Rating Scale (WURS) (Ward et al., 1993). This scale is a condensed version of the of the 61-item original scale to retrospectively assess ADHD symptoms in childhood. The two versions of the WURS have shown good