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Evidence for an agitated-aggressive syndrome in early-onset psychosis correlated with antisocial personality disorder, forensic history, and substance use disorder

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ABSTRACT

Objective: Agitation, aggression, and violence are increased in psychotic disorders. Additionally, an earlier age at onset may be associated with aggressive behavior. However, the relationship of age at onset, an agitated-aggressive syndrome as measured with the Positive And Negative Syndrome Scale for Schizophrenia - Excited Component (PANSS-EC), and its potential correlates in first-episode psychosis (FEP) has not been studied.
Method: This study assessed the association between age at onset, an agitated-aggressive syndrome, and its potential correlates in a prospective sample of 52 FEP patients with early-onset and adult-onset followed up for 12 months.
Results: Twenty-six patients conformed to the criteria of early-onset psychosis. Early age at onset was associated with antisocial personality disorder ($p = 0.004$; $\varphi_c = 0.39$), a history of legal involvement ($p = 0.005$; $\varphi_c = 0.39$), and higher rates of lifetime substance use disorder (SUD; $p = 0.002$; $\varphi_c = 0.42$). Early-onset patients had significantly higher PANSS-EC scores over the course of observation ($F(1,44.4) = 5.39$; $p = 0.025$; $d = 0.656$), but no significant group differences emerged for the remaining PANSS subscores. PANSS-EC scores were correlated positively with antisocial personality disorder and forensic history at 6 weeks, 3 months, 6 months, and 12 months, and with lifetime substance use disorder at 3 months and 6 months.
Conclusions: Patients with early onset psychosis may have increased levels of agitation/aggressiveness, and, more likely, antisocial personality disorder, forensic history, and lifetime substance use disorder. These variables were linked to suicidality, aggressiveness, and involuntary treatment.

1. Introduction

Agitation, aggression, and violence are increased in patients with psychotic disorders (Angermeyer, 2000; Arseneault et al., 2000; Wallace et al., 2004; Hodgins, 2008; Elbogen and Johnson, 2009; Khalid et al., 2012). They can appear very early in the course of illness (Spidel et al., 2010; Khalid et al., 2012; Starling et al., 2013), first-episode psychosis (FEP) patients often present with a history of legal involvement and violence at first contact with psychiatric services (Payne et al., 2006; Dean et al., 2007; Huber et al., 2012), and there is a considerable amount of aggressive incidents afterwards (Milton et al., 2001).

In previous studies, our group found evidence for the presence of an agitated-aggressive syndrome predicting severe aggression, suicidality, and involuntary treatment in FEP patients (Huber et al., 2012). Furthermore, we found increased levels of an agitated-aggressive syndrome already present in at-risk mental state (Huber et al., 2014). However, the association between an agitated-aggressive syndrome and onset of illness in psychotic disorders is not yet sufficiently understood.

At present, there is evidence that early onset may be associated with increased prevalence of neurological soft signs (Biswas et al., 2006; White et al., 2006; Biswas et al., 2007), more negative symptoms (Ballageer et al., 2005; Pencer et al., 2005) and substance use (Pencer et al., 2005; Compton et al., 2009; Large et al., 2011; Leeson et al., 2012), lower levels of pre-morbid functioning, a longer duration of untreated psychosis (Ballageer et al., 2005; Schimmelmann et al., 2007), and increased cognitive deficits (Rajji et al., 2009). For male patients with bipolar I disorder, representing only a small part of the heterogeneous spectrum of diagnoses that constitute FEP, there is evidence that an earlier onset may be associated with childhood antisocial behavior (Kennedy et al., 2005). Additionally, there is evidence for an association between aggressive behavior and earlier age at onset in patients with schizophrenia spectrum and bipolar I disorder (Chang and Lee, 2004).

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Despite this first evidence, there are currently no published data concerning the relationship of age at onset, an agitated-aggressive psychopathological syndrome, and its potential correlates in first-episode psychosis.

1.1. Aims of the study

To assess the association of age at onset with an agitated-aggressive syndrome, as measured using the Positive and Negative Syndrome Scale for Schizophrenia – Excited Component (PANSS-EC), and its potential correlates in a prospective sample of first-episode patients with early-onset and adult-onset psychosis followed up for 12 months.

2. Methods

2.1. Context and sample

This study presents post-hoc analyses from observational data obtained through clinical diagnostics and treatment of FEP patients at the Department of Psychiatry, University Medical Centre Hamburg-Eppendorf (UKE Hamburg), Germany, from January 2005 to December 2005. All in- and outpatients, aged 14 to 30 years, with a first psychotic episode (Mrazek and Haggerty, 1994), symptom duration > 1 week (Yung et al., 2004), and a history of no longer than 6 months of specific treatment were included into the analyses. Diagnostic inclusion criteria were a DSM-IV (APA, 2000) diagnosis of schizophrenia, schizophreniform disorder, schizoaffective disorder, brief psychotic episode, delusional disorder, substance induced psychotic disorder, psychotic disorder not otherwise specified, bipolar I disorder with psychotic symptoms, or major depressive episode with psychotic symptoms. Exclusion criteria were the diagnosis of a psychotic disorder due to a medical illness according to DSM-IV, a history of pharmaceutical antipsychotic treatment longer than 4 weeks, insufficient knowledge of German, and mental retardation (IQ < 70). As all data were gathered during clinical routine treatment, no informed consent was necessary for this analysis. The study was conducted in accordance with all local and national regulations, and the local ethics committee approved the study protocol (OB-026/06).

During the study period, 55 patients (14 outpatients, 39 inpatients) conforming to the in- and exclusion criteria were treated at the Department of Psychiatry, UKE Hamburg. Data from 3 patients had to be omitted due to missing data at baseline, and thus the final sample included 52 patients.

2.2. Assessments and measures

After baseline assessment (BL), the clinical protocol included follow-up visits at 6 weeks, 3 months, 6 months, and 12 months. Data on patient history and sociodemographic data were collected using the Early Psychosis File Questionnaire (EPFQ; Conus et al., 2007) and the Symptom Onset in Schizophrenia Scale (SOS; Perkins et al., 2000). Diagnoses were established using the Structured Clinical Interview for the DSM-IV (SCID; Wittchen et al., 1997). The Positive and Negative Syndrome Scale (PANSS; Kay et al., 1987) was used to assess psychopathology. Inter-rater reliability showed satisfactory values (PANSS total score: $\kappa = 0.68$).

2.3. Definitions

Duration of untreated illness (DUI), duration of untreated psychotic prodrome (DUPP), and duration of untreated psychosis (DUP) were assessed using the SOS. Age at onset was defined as the age when first sustained positive psychotic symptoms started and dichotomized in early-onset (onset ≤ age 18) and adult-onset (onset > age 18) (AACAP, 2001; Ballageer et al., 2005). Ratings were re-examined at each follow-up visit and case conference and adapted when new information on symptom onset became available.

The severity of an agitated-aggressive syndrome was measured using the PANSS-EC (theoretical range: 4 to 28), composed of the PANSS items P4 (excitement), P7 (hostility), G8 (uncooperativeness), and G14 (poor impulse control). The PANSS-EC subscore was established as an independent rating scale by Lindenmayer et al. (2004) and has since been repeatedly applied in trials evaluating acute agitation and aggression in patients with schizophrenia spectrum disorders (Turczynski et al., 2004; San et al., 2006; Lambert et al., 2008). A high linear correlation between the PANSS-EC and a Clinical Global Impressions Severity scale for Aggression (CGI-A) has been demonstrated (Huber et al., 2008). PANSS Positive, PANSS Negative, PANSS Disorganized, PANSS-EC, and PANSS Anxiety/Depression subscores were calculated according to Davis and Chen (2001). The factor structure of the PANSS-EC score from this publication has been confirmed for patients with chronic schizophrenia, schizophreniform disorder, schizoaffective disorder (Levine and Rabinowitz, 2007), and for patients with recent-onset psychosis (Wolthaus et al., 2000; Emsley et al., 2003).

Forensic history was measured using the EPFQ. As part of this self-report questionnaire, patients were asked if they had ever had contact with the legal system for any form of conviction. Lifetime substance use disorder (SUD), divided into substance abuse and substance dependency, and antisocial personality disorder were diagnosed using SCID (Wittchen et al., 1997).

2.4. Analysis plan

The study protocol for the current post-hoc analyses was designed to examine if age at onset in FEP is associated with an agitated-aggressive syndrome as measured via the PANSS-EC at baseline and over a period of up to 12 months.

2.4.1. Main analysis

To address this issue, we compared the time course in the early-onset and adult-onset groups using linear mixed-model analyses based on compound symmetry by reason of best variance-covariance matrix (Tabachnick and Fidell, 2006). To test if potential differences concerning an agitated-aggressive syndrome are specific, we performed similar analyses for the remaining PANSS subscores.

2.4.2. Exploratory analyses

Further analyses were conducted to examine the early-onset and adult-onset groups for baseline differences in variables potentially associated with an agitated-aggressive syndrome. Group comparisons were performed using analysis of variance (ANOVA) when the dependent variable was continuous and assumptions for normality were met, Mann-Whitney *U* test when the dependent variable was continuous and normality assumptions were violated, and chi-square analysis (χ^2) when the dependent variable was categorical. DUP values were analyzed after logarithmic transformation because of a significantly positively skewed distribution. To analyze if differences in diagnostic distribution could explain our findings, group differences between patients with schizophrenia-spectrum disorders and with other psychotic disorders for PANSS-EC scores from all visits were examined. To assess if other variables with baseline differences (i.e., antisocial personality disorder, forensic history, and lifetime SUD) were associated with PANSS-EC scores in our patient group, we performed Spearman correlation analyses for these variables with PANSS-EC scores at all visits. This approach was chosen because our sample size did not support more advanced multivariate analyses (Tabachnick and Fidell, 2006). For exploratory analyses, no corrections for multiple comparisons were applied.

All tests of significance were 2-tailed, and *p*-values < 0.05 were considered significant. Effect size Cramer's φ was defined as small (φ = 0.1–0.29), medium (φ = 0.3–0.49), and large ($\varphi \geq 0.5$). Effect size

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