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The course of negative symptoms in first-episode schizophrenia and its predictors: A prospective two-year follow-up study

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ABSTRACT

Aims: This study aimed to investigate the course of negative symptoms and its stability over a two-year period following a first-episode schizophrenia (FES) and the possible predictors of higher severity in this symptomatology after this period.
Methods: In this longitudinal two-year prospective follow-up study we included 268 patients with a FES, according to DSM-IV. Analysis of variance was conducted in patients who completed the full follow-up to study changes in negative symptoms over three visits. Regression analyses were conducted to show correlates and potential predictors of negative symptoms at two-year follow-up.
Results: There was a significant effect for time in negative symptomatology, which was less severe at one-year follow-up after a FES and remained stable up to two years (*Time 1* > *Time 2* > *Time 3*); $F(2,151) = 20.45$, $p < 0.001$. Poorer premorbid adjustment ($p = 0.01$) and higher negative symptoms at baseline ($p < 0.001$) made a significant contribution to the changes in the negative symptoms severity at two-years after a FES ($R^2 = 0.21$, $p < 0.001$).
Conclusions: We found a reduction in the negative symptomatology at one-year after a FES. This change remained stable at two-year. Our results suggested that the presence of this symptomatology early in the course of the illness, together with a poorer premorbid adjustment, predict more severe negative symptoms at mid-term outcome.

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1. Introduction

Negative symptoms, together with positive, cognitive and affective symptoms, are well known to be a core feature of schizophrenia and other related disorders (Strauss et al., 2013). Negative symptomatology has been demonstrated to be the most relevant predictor of increased future socio-occupational dysfunction and poorer quality of life (Bernardo et al., 2014c; Chue and Lalonde, 2014; Bobes et al., 2010). Thus, negative symptoms and the resulting loss in productivity are responsible for much of the world-wide personal and economic (direct and indirect) burden of schizophrenia (Sarkar et al., 2015; Bernardo and Mezquida, 2014b). However, its assessment and treatment is still a major challenge (Stahl and Buckley, 2007; Aleman et al., 2016). Knowledge about course of schizophrenia after a first-episode could help clinicians to develop more effective interventions and improve treatment outcomes (Austin et al., 2013). In this regard, the early identification of patients who will develop more severe negative symptoms after a first-episode schizophrenia (FES) might foster research progress on treatment of those symptoms for which an early intervention might be helpful (Melle et al., 2008; Ventura et al., 2015; Bernardo and Bioque, 2014a).

Two types of negative symptoms have been described for schizophrenia: primary and secondary negative symptoms. Primary negative symptoms are inherent to the disease process itself and are stable. They are distinct to secondary negative symptoms, which appear due to other causes, such as positive symptoms, medication side-effects, social deprivation or substance abuse (Bernardo et al., 2007; Buchanan, 2007; Kirkpatrick et al., 1989). Patient subgroups with predominant and persistent negative symptoms differ across a range of clinical features, including treatment profile, cognitive performance, neurological correlates, prognostic course and functional outcome (Kirkpatrick et al., 2001; Kirkpatrick and Galderisi, 2008).

Approximately 20–40% of patients diagnosed with schizophrenia have persistent or deficit negative symptoms (Makinen et al., 2008). This symptomatology can occur at any stage of the illness (An der Heiden et al., 2016). However, in first-episode psychosis (FEP), it is difficult to diagnose due to the predominance of positive symptoms. Notwithstanding, the evidence is mounting that even in these early stages of the illness, negative symptoms are often a core feature (Ventura et al., 2015) and are present in about one third to one-half of FES (Hovington et al., 2012). These symptoms can be present during and between episodes of symptom exacerbation. FEP patients who demonstrate more negative symptoms at baseline show significantly worse functioning when they are assessed again at one year in comparison to FEP patients without negative symptoms (Sarkar et al., 2015; Hovington et al., 2012). Follow-up studies of early course schizophrenia and related disorders patients have found that if negative symptoms are also present at baseline, they tend to be stable and persistent, but can fluctuate in severity (Ventura et al., 2015). Knowing early prevalence rates and factors associated with negative symptomatology would help provide general benchmarks for identifying negative symptom severity. This would help to prevent long term disability in early stages of the illness.

The present longitudinal prospective study is aimed to (1) study the differences and stability between negative symptoms severity in patients after a FES at the baseline visit, at one-year and at two-year follow-up, and (2) identify early-course predictors of higher negative symptom severity during a two-year follow-up period after a first-episode. We hypothesized that there would be a decreased severity in the negative symptomatology during the first years after a first-episode psychosis, and that there would be a set of clinical and/or demographical main predictors related to negative symptom severity two years after a first episode.

2. Method

This study is part of the project "Phenotype-genotype interaction. Application of a predictive model in first psychotic episodes, FIS PI080208" (known as the PEPs study, Spanish abbreviation), involving 16 Spanish mental health research centres. A complete description of the protocol for the PEPs study has been published previously (Bernardo et al., 2013; Cuesta et al., 2015; Pina-Camacho et al., 2016).

2.1. Participants

335 patients with a first-episode of psychosis were recruited within the PEPs study following inclusion criteria: (1) aged 7–35 years at the time of first evaluation, (2) duration of psychotic symptoms not exceeding one year, (3) meeting diagnostic criteria for schizophrenia or schizophrenia spectrum disorders (schizophreniform, schizoaffective or brief psychotic disorder, as well as psychotic disorder not otherwise specified), (4) being fluent in Spanish, and (5) providing their written informed consent. In case of children under 16 years of age, parents or legal guardians gave written informed consent before the beginning of their participation in the study. The exclusion criteria were: mental retardation according to the DSM-IV (including both an IQ below 70 and impaired functioning); history of head injury with loss of consciousness, and somatic pathology with intellectual impact. The study was approved by the research ethics committees of all participating clinical centres.

To ensure more homogeneous sample diagnoses, we only included those patients with non affective FES, as we considered affective first-episode patients a subgroup displaying several specific characteristics in terms of clinical course, functional outcome and antipsychotic treatment. We also excluded those patients with toxic psychosis, due to the fact that its aetiology could be different from other organic psychosis diagnoses. Thus, from the initial 335 patients, our final sample size comprised 268 patients with a first-episode of schizophrenia or schizophrenia spectrum disorder. At two-year follow-up, the sample consisted of 161 patients, which represented an attrition rate of 40%. 107 patients discontinued or dropped out of the study, particularly due to a loss of follow-up or refusing re-evaluation. There were two patients without clinical assessment at one-year follow-up but with clinical assessment at two-year follow-up. We decided not to exclude these individuals from the analyses.

2.2. Study design

This longitudinal two-year prospective follow-up study presents clinical measures from 3 different assessments/visits: baseline, one-year and two-year follow-up. At baseline, a complete evaluation was performed collecting: demographic data, clinical scales, family environment, premorbid adjustment scales, age at onset of the illness (early onset = younger than 18), pharmacological treatment, parental socioeconomic status (SES), level of education and substance use. Clinical, functional and disability scales, antipsychotic medication treatment and substance use were collected again at 1 and 2-year visits. To ensure a correct diagnosis, we focused on information from a structured interview at the two-year visit.

2.3. Clinical assessment measures

Demographic data were collected for all patients. Diagnoses were determined according to the DSM-IV criteria (American Psychiatric Association, 1994) according to the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) (American Psychiatric Association, 1994) with the SCID-I (Williams et al., 1992) or the Kiddie-SADS (Kaufman et al., 1997) depending on age. Clinical symptomatology was assessed using the Spanish validated version of the Positive and Negative Syndrome Scale (PANSS) (Kay et al., 1987; Peralta and Cuesta, 1994). The Spanish validated version of the Montgomery-Asberg Depression Rating Scale (MADRS) (Lobo et al., 2002; Montgomery and Asberg, 1979) and the Young Mania Rating Scale (YMRS) (Young et al., 1978) were used to measure affective symptoms.

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