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Original article

Negative symptom subgroups have different effects on the clinical course of schizophrenia after the first episode: A 24-month follow up study

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ABSTRACT

Objective: The aim of this study was to assess the factor structure of negative symptoms in first-episode schizophrenia (FES), and to examine the relationship of these factors with clinical course and functioning of patients during the two-year follow up.
Method: We assessed 174 drug-naïve patients with FES using Brief Psychiatric Rating Scale-Expanded (BPRS), Scale for the Assessment of Negative Symptoms (SANS), Scale for the Assessment of Positive Symptoms (SAPS), and Global Assessment of Functioning (GAF) and a cognitive battery at admission. The scales were repeated monthly during follow up. We recorded the patients' functioning levels, remission, and work status after 12 and 24 months.
Results: A two-factor structure was found at the baseline, whereas one factor was found after 12 and 24 months. Expressive deficit (ED) factor consisted of alogia and blunted affect, and motivation-pleasure deficit (MPD) factor consisted of avolition and anhedonia. ED factor was related to earlier onset and remission, and it was negatively correlated with duration of education and cognitive test scores. MPD factor was related to duration of untreated psychosis, family history of schizophrenia, and work status, and it appeared as the only independent variable that contributed to the baseline GAF score in linear regression analysis.
Conclusion: Our findings suggest that the factors have different aetiologies and impacts on the clinical course of schizophrenia and functioning after FES.

1. Introduction

Previous factor analytic studies that examine the underlying structure of schizophrenia symptoms show that negative symptoms represent a domain separate from others [22,34]. The heterogeneity of negative symptoms implies that there may be subgroups with discrete aetiologies that are related to premorbid and clinical variables differently, such as the level of premorbid adjustment, duration of untreated psychosis, and family history of psychosis. However, it is still not clear if patients with differing negative symptom subgroups can be identified. Studies examining the factor structure of negative symptoms consistently find a multidimensional construct, typically including two factors: one consisting of alogia and blunted affect, and representing expressive deficit (ED); the other consisting of avolition-apathy and anhedonia-asociality, and representing motivation-pleasure deficit (MPD) [22–24,35,37,43]. Strauss et al. [43] called the first factor diminished expression (DE) and the second one avolition-apathy (AA). Researchers reported that these factors significantly differed in clinically relevant external validators that included measures of functional outcome, premorbid adjustment, and clinical course. In addition, patients with AA had more severe psychotic symptoms, higher levels of anhedonia, more frequent hospitalizations, and greater social cognitive impairment than patients with DE. Patients with AA were also more likely to have a family member hospitalized for psychiatric reasons, more likely to have poorer premorbid social adjustment in childhood, and were less likely to be gainfully employed than patients with DE. The DE group had a greater likelihood of abrupt onset of psychosis compared with the AA group, and they were also hospitalized for longer durations. Bell et al. [4] reported that expressive deficit factor was more closely related to neurocognitive impairments.

It is important to study the relationship of negative symptom subgroups with clinical course in a sample of patients

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with first-episode schizophrenia because antipsychotics and chronicity can affect the severity of negative symptoms. For example, antipsychotics can cause secondary negative symptoms such as restricted affect, amotivation, or increase the level of existing primary negative symptoms [33]. Additionally, as the duration of time with the disorder increases, repeated relapses and hospitalisations may increase the level of existing negative symptoms because they contribute to the isolation of the patient from the environment. Malla et al. [32] designed the only cross-sectional study that analysed variables related with different subgroups of negative symptoms in first-episode psychosis. However, less than half of their sample was drug-naïve, and only 70% of the patients were diagnosed as having a schizophrenia spectrum disorder. They reported three factors of negative symptoms including flat affect/alogia, avolition/anhedonia and inattention/disorganization. The authors also reported a relationship between the duration of untreated psychosis (DUP) and avolition/anhedonia factor, and a relationship between the age of onset and blunted affect/alogia factor.

A drug treatment with specific effects on negative symptoms has not yet been developed. Decreasing the heterogeneity of negative symptoms is the first step for future studies in becoming more focused. Distinguishing negative symptom subgroups may uncover discrete etiologic processes, and may help the development of more specific treatment options. To do this, we investigated the underlying construct of observable negative symptoms in a sample of patients with first-episode schizophrenia (FES). Based on the available literature, we hypothesized that two distinct negative-symptom factors would appear in the analysis. We also hypothesized that ED factor would be related to cognitive deficits at baseline, and MP factor would be related to functional outcomes and duration of untreated psychosis.

2. Participants and methods

2.1. Participants

Participants were recruited from an ongoing first-episode schizophrenia follow up project in Istanbul Faculty of Medicine. Patients who met the Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-IV) diagnosis of schizophrenia criteria through a Structured Clinical Interview (SCID I) [13] were re-evaluated at a consensus meeting to incorporate clinical and SCID data. A patient was considered to be in a first-episode of psychosis if all of the following conditions were met: no history of affective or non-affective psychosis, no antipsychotic treatment longer than 15 days, and no inpatient care. Patients with any other DSM-IV Axis I diagnoses or serious medical illness were excluded. All hospitalized patients with FES were invited to the follow up study. Eight outpatients with FES were also included in the study. The diagnosis of schizophrenia was verified through re-administration of the SCID six months after admission. We recruited 174 people to this prospective naturalistic study. After completing the clinical assessments at admission, 24 patients refused to participate in the follow up evaluations or did not attend the first outpatient visit, 11 patients moved to other cities, 35 patients dropped out before 12 months, and 12 patients did not fulfil the minimum of one year follow up criterion at the time of statistical analyses. Two patients committed suicide and another patient died of an unknown cause during the 24-month follow up.

After the baseline procedures, the patients received adequate antipsychotic treatment (maintenance dosage equivalent to at least 3 mg/day risperidone). During the follow up, antipsychotic drugs were changed to or combined with other antipsychotics due to reasons like inefficacy and adverse effects. Compliance with treatment was evaluated only with consideration of the first six months of follow up. Patients who used less than the prescribed dose or completely skipped their medication for 10 consecutive days were regarded as "non-compliant".

The Ethical Committee of Istanbul Faculty of Medicine approved the study protocol, and the patients gave informed consent. All patients were white Turkish people who lived in Istanbul.

2.2. Clinical assessments

The patients were first evaluated at admission when they were drug-naïve, then at monthly visits using the Brief Psychiatric Rating Scale-Expanded (BPRS) [31], the Scale for the Assessment of Positive Symptoms (SAPS) [2], and the Scale for the Assessment of Negative Symptoms (SANS) [1]. All item values were assigned by two trained raters. Inter-rater reliabilities for the BPRS, SANS, and SAPS total scores were acceptable ($\kappa = 0.78$, $\kappa = 0.76$, and $\kappa = 0.83$ respectively). The Premorbid Adjustment Scale (PAS) [6] was used to assess premorbid functioning. PAS measures levels of functioning in terms of social accessibility-isolation, peer relationships, school performance, adaptation to school, and the capacity to establish social-sexual relationships. We took childhood (up to 11 years) and adolescence (12–15 years) into consideration. The patients were subjected to a cognitive test battery consisting of the Rey Auditory-Verbal Learning Test (RAVLT) [40], Stroop Test [18], Wisconsin Card Sorting Test (WCST) [21], Digit Span test [48], Continuous Performance Test (CPT) [41], Trail Making Test (TMT) [39], and the n-back test [25] when they were drug-naïve. RAVLT was used to assess verbal learning and memory. Performance measures were the total number of correctly recalled words in trials I to V (verbal learning) and in the delayed recall trial (secondary verbal memory). The Stroop Test measures selective attention and processing speed, as well as cognitive flexibility and executive functions. Number of commission errors and time difference between color and word reading tasks comprised the performance measures. The digit span test measures short-term auditory recall. Dependent variables were the maximum numbers of correctly recalled digits in the digit span forward and backward tests. The WCST was used to measure executive functioning. Dependent variables were the number of correct answers and sets completed. CPT was used to measure the sustained attention. Hit rate was the dependent variable in CPT. TMT-A measures the processing speed and TMT-B measures executive functions. Participant is evaluated on the basis of the duration of time that she/he connects the trail. N-back test measures working memory. The reaction time of correct trials and accuracies in 0-back and 2-back tests were dependent variables. The methods used to score these assessments were presented in detail in our prior publication [45]. The cognitive test battery was only administered to the last 53 participants because it was a late addition to the study design.

We described remission in accordance with the criteria that was introduced by Andreasen et al. [3]. The work/study status was decided based on information obtained during direct interviews with the patients and their families and from social worker reports. The work/study status was evaluated at three different time periods: one month prior to admission, and at the first and second year of follow up. Paid workers and full-time students were regarded as working if they were able to show a stable performance for at least six months of the evaluated year. The date of the first positive symptoms was identified by the senior psychiatrist (AU) on the basis of a best-estimate approach using the data gathered from multiple sources such as patient and family interviews, and medical records. We defined the DUP as the time from the onset of positive symptoms until the date of adequate antipsychotic treatment.