European Psychiatry 30 (2015) 995–1001

Contents lists available at ScienceDirect

European Psychiatry

journal homepage: http://www.europsy-journal.com

Original article

Differential impacts of duration of untreated psychosis (DUP) on cognitive function in first-episode schizophrenia according to mode of onset

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ARTICLE INFO

Article history:
Received 22 May 2015
Received in revised form 17 August 2015
Accepted 18 August 2015
Available online 24 October 2015

Keywords:
Cognitive function
Duration of untreated psychosis (DUP)
First-episode
Mode of onset
Prospective follow-up
Schizophrenia

ABSTRACT

Background: The mode of onset and the course of schizophrenia illness exhibit substantial individual variations. Previous studies have pointed out that the mode of onset affects the duration of untreated psychosis (DUP) and clinical outcomes, such as cognitive and social functioning. This study attempted to clarify the association between the DUP and clinical features, taking the different modes of onset into consideration, in a prospective longitudinal study examining patients with first-episode schizophrenia.
Methods: This study was conducted in six areas of Japan. Patients with first-episode schizophrenia were followed for over 18 months. Cognitive function, psychopathology, and social functioning were assessed at baseline and at 6, 12, and 18-month follow-up points.
Results: We identified 168 patients and sufficient information was available to determine the DUP and the mode of onset for 156 patients (92.9%): 79 had an acute onset, and 77 had an insidious onset. The DUP was significantly associated with quality of life (QOL), social functioning, and cognitive function at most of the follow-up points in the insidious-onset group. The DUP and negative symptoms at baseline were significant predictors of cognitive function at the 18-month follow-up in the insidious-onset group.
Conclusions: The present results further support the hypothesis that the DUP affects QOL, social functioning, and cognitive function over the course of illness, especially in patients with an insidious onset. Effective strategies for detecting and caring for individuals with insidious onset early during the course of schizophrenia will be essential for achieving a full patient recovery.

1. Introduction

The mode of onset and the course of schizophrenia illness show substantial individual variations. The mode of onset is usually classified into three categories according to the Personal and Psychiatric History Schedule [14,26]: sudden, acute, and insidious onset. These classifications were also used in a large epidemiological study, Aetiology and Ethnicity in Schizophrenia and Other Psychoses (AESOP) [21].

Some studies have pointed out that the mode of onset might affect the length of the duration of untreated psychosis (DUP) [3,19,21]. Meta-analysis studies have demonstrated a modest association between the DUP and clinical features [19,27], and the mode of onset might contribute to this relationship as a confounding factor.

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http://dx.doi.org/10.1016/j.eurpsy.2015.08.004
0924-9338/

Cognitive impairments have been shown to predict functional outcomes [9]. Some previous studies have revealed that a prolonged DUP was associated with more severe cognitive impairments in patients with schizophrenia [5,6], while others have failed to show such a relationship [8,28]. The results obtained so far are thus controversial.

The aim of this study was to clarify the association between the DUP and clinical features, taking the different modes of onset into consideration, in a prospective longitudinal study examining patients with first-episode schizophrenia in Japan. To eliminate the influence of the mode of onset on the DUP and its relations to clinical features, we categorized the mode of onset into acute onset (including sudden onset) and insidious onset and analyzed the patients accordingly. We hypothesized that (1) the DUP of the acute-onset group would be shorter than that of the insidious-onset group, (2) the symptomatic and functional status of the acute-onset group would be better than those of the insidious-onset group at any of the follow-up points, (3) the DUP would have different effect on clinical status in each group, and (4) the DUP would contribute to cognitive function at an 18-month follow-up examination.

2. Methods

2.1. Setting

The current study was conducted in six areas of Japan (Miyagi, Tokyo, Toyama, Nara, Kochi, and Nagasaki) at six university hospitals, three general hospitals, and five psychiatric hospitals between July 1, 2008, and March 31, 2011. All the participants provided informed consent, and the study was approved by the Ethics Committees of the institutions that were involved. This study complied with the ethical guidelines for research involving human participants, as set out in the Declaration of Helsinki in 1995 (revised in Edinburgh in 2000).

2.2. Participants

The subjects fulfilled the following inclusion criteria: (i) age between 16 to 55 years at the time of their first visit to the hospital (the patients' first time seeing psychiatrists for their psychosis); (ii) meeting the ICD-10 criteria for schizophrenia, schizotypal and delusional disorders (F2); (iii) no previous adequate treatment for psychosis (antipsychotic medication for 2 weeks or more); that is, treatment was sought for the first-episode of illness; and (iv) no history of a psychotic condition associated with substance-related disorders, mental retardation, and/or organic diseases. Subjects were outpatients and inpatients with first-episode schizophrenia. All the diagnoses were made by trained psychiatrists at the time of each patient's first visit to a hospital. The intra-class correlation among the 8 hospitals was 0.98 (95% confidence interval, 0.97-0.99) [13]. The intra-class correlation among the 27 participants was 0.96(95% confidence interval, 0.93-0.98) [13].

2.3. Measures

The subjects were interviewed by certified clinical psychologists in charge of each case at the time of their first visit and at 6-month, 12-month, and 18-month follow-up examinations. Global social functioning was measured using the Global Assessment of Functioning (GAF) [2]. The overall severity of disease was measured using the Clinical Global Impression (CGI) [11]. The doses of antipsychotic drugs were calculated according to their chlorpromazine equivalent (CP mg equivalent). Psychiatric symptoms were measured using the Positive and Negative Syndrome Scale (PANSS) [16,31]. Quality of life (QOL) was evaluated based on the mean WHOQOL-26 score [29], in which a higher score indicates a better QOL. Cognitive function was evaluated using the Schizophrenia Cognition Rating Scale (SCoRS) [15,17]. The SCoRS was an 20-item interview-based assessment of cognitive deficits affecting day-to-day functioning, in which a higher score reflects severer impairment. We used the global rating score of the SCoRS. We evaluated social functioning using the total score of the Social Functioning Scale (SFS) [4,23], in which a higher score indicates a higher level of functioning. The Premorbid Adjustment Scale (PAS) [1,25] and the Japanese Adult Reading Test (JART) [20,22] were measured to assess premorbid conditions. The PAS indicates premorbid functioning at two different stages of life prior to the onset of illness: childhood (6-12 years) and adolescence and young adulthood (13-21 years). A higher score indicates a poorer premorbid functioning. The reliability and validity of Japanese version of the scales used in this study were described elsewhere [15,20,25,31].

The Personal and Psychiatric History Schedule [26] divides the mode of onset into 3 modes: (a) sudden (psychotic symptoms appeared within days of first noticeable behavioral changes); (b) acute (psychotic symptoms appeared within one month of first noticeable behavioral changes); and (c) insidious (psychotic symptoms appeared incrementally over a period of more than one month since the first noticeable behavioral change). In a previous study [12], patients were grouped into two categories: acute (comprising the sudden and acute modes) and insidious; we adopted this methodology in the current study. The DUP was defined as the interval (in months) between the onset of psychotic symptoms and the first prescription of neuroleptics for psychosis. The data was obtained by an interview with the patients and their families [32,33].

2.4. Statistical Procedures

A four-step analysis was conducted. For the first step, the baseline characteristics of the acute-onset and the insidious-onset groups were compared using an unpaired t-test, the Mann Whitney U-test, and the chi-square test. For the second step, the symptomatic and functional status of the two groups at the follow-up examinations (baseline and 6, 12, and 18 months) were compared using a multivariate analysis of variance (MANOVA). The Bonferroni adjustment was used for multiple comparisons. For the third step, to estimate the relationships among the symptomatic and functional status at the follow-up points and the DUP according to the different modes of onset, the Pearson product-moment correlation coefficient was used because of the longitudinal design of this step. For the final step, we used a multiple linear regression analysis to estimate the factors at baseline that contributed to cognitive function at the 18-month follow-up.

Regarding the multiple linear regression analysis, the SCoRS score at the 18-month follow-up point was used as a dependent variable, and the GAF, CGI, dose of antipsychotics, PANSS, and WHOQOL-26 at baseline were used as independent variables. The PAS was included as a covariate in the analysis because a study by Marshall et al. [19] pointed out that premorbid adjustments might be related to the length of the DUP. The SFS was excluded from the independent variables because an improvement in cognitive function (cause) affects the improvement in social function (effect) [10]. The variables were excluded using a stepwise selection. When controlling for the effects of PAS, forward variable selection was used. To evaluate multicollinearity, the variance inflation factor (VIF) was performed. A VIF value of 10 or more indicates a high collinearity and inflated standard errors. Because the DUP did not have a normal distribution, as noted in several previous studies, the DUP was transformed to its common logarithm. Analyses were