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Symptomatic and functional remission of subjects at clinical high risk for psychosis: A 2-year naturalistic observational study

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ABSTRACT

Background: The aim of this study was to assess the frequency and predictors of symptomatic and functional remission in individuals at clinical high risk (CHR) for psychosis at 1–2 years of follow-up.
Methods: Help-seeking CHR individuals with symptomatic (Scale of Prodromal Symptoms (SOPS) positive scores <3) and functional (Global Assessment of Functioning (GAF) score >60) (CHR-R) remission at 12–24 months were compared to non-remitted individuals (CHR-NR) regarding baseline and treatment characteristics, symptom changes and predictors. Time to full remission was compared with that of symptomatic remission only.
Results: Of 73 individuals, 29 (39.7%) achieved full remission; 44 (60.3%) did not. Compared to CHR-NR individuals, CHR-R individuals had lower baseline SOPS positive symptoms ($p = 0.017$), antipsychotic use ($p = 0.004$), antipsychotic chlorpromazine dose equivalents ($p = 0.001$) and anxiolytic use ($p = 0.004$). In survival analyses, the estimated full remission rate was 48.3% (95% confidence interval (CI) = 36.2–61.9) and symptomatic remission rate was 67.5% (CI95 = 55.4–79.2). Time to full remission was longer than time to symptomatic remission ($p = 0.017$). Linear mixed-effect models revealed significantly greater improvements from 6 months onward in CHR-R subjects compared to CHR-NR subjects regarding SOPS positive symptoms ($p = 0.003$), highest SOPS positive symptom ($p < 0.001$) and GAF scores ($p = 0.004$). Examining baseline predictors, time to full remission was significantly longer in patients with higher SOPS positive scores ($p = 0.017$).
Conclusions: More stringent remission criteria that include functional status in addition to attenuated positive symptom severity should be applied to CHR subjects. Furthermore, more attention should be given to CHR individuals with highly positive prodromal symptoms at baseline.

1. Introduction

Because early intervention in psychosis is hoped to improve the clinical prognosis, the identification of individuals who might develop psychosis has become a major objective for clinicians and researchers (Correll et al., 2010; Fusar-Poli et al., 2013a, 2013b; Stafford et al., 2013; van der Gaag et al., 2013). The concept of 'clinical high risk' (CHR) or 'ultra-high risk' was developed to identify individuals showing symptoms and longitudinal studies have validated the predictive value of established CHR and UHR criteria (Fusar-Poli et al., 2013a, 2013b). However, recent studies have shown that the transition rates to psychosis have been decreasing (Yung et al., 2007; Fusar-Poli et al., 2012), therefore, the characteristics and outcomes of CHR individuals not converting to psychosis have gained increasing attention.

Recent studies on remission in CHR individuals have revealed that CHR nonconverters are a heterogeneous group composed of individuals who continue having prodromal symptoms as well as of individuals who lost their CHR status based on the symptomatic remission of attenuated psychotic symptoms (Addington et al., 2011; Schlosser et al., 2012). However, since CHR criteria are not the only determinant of outcome, it is of high importance from a clinical and research standpoint to determine the diagnostic and symptomatic as well as functional outcome of non-converting and remitted CHR individuals. Recent studies have documented that early impaired functioning appears to be a risk factor for psychosis (Velthorst et al., 2010; Cornblatt et al., 2012;

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Nieman et al., 2013; Valmaggia et al., 2013). Addington et al. (2011) indicated that CHR nonconverters remained at a lower level of functioning than healthy comparison subjects, despite significant symptomatic improvement over 2.5 years. Previous studies of CHR individuals reported that remission indicates that the individual 'no longer meets CHR criteria' (Lemos-Giráldez et al., 2009; Simon and Umbricht, 2010; Ziermans et al., 2011). However, the exact meaning of 'not longer meeting CHR criteria' is not well defined. For example, genetic risk with deterioration as a subtype of CHR criteria is defined without considering aspects of severity or persistence of (attenuated) psychotic symptoms. It is possible that while functioning improves, attenuated psychotic symptoms could remain stable or worsen. Likewise, patients could show symptomatic improvement, but have functional decline. These scenarios underscore the complexities of assessing remission from a CHR state. Therefore, considering both the symptomatic and functional aspects of outcome offers a more appropriate means to describe remission from CHR status as well as remission in general.

The aims of the present study were to 1) examine the clinical and functional characteristics of nonconverters; 2) investigate the remission rate and longitudinal changes in clinical symptoms and functioning with stringent remission criteria; and 3) identify predictors of the time to remission from the CHR state. We hypothesized that many CHR nonconverters will not remit both symptomatically and functionally, and that full remission rates would be significantly lower than symptomatic remission only. We further expected that higher positive prodromal symptom severity and lower functioning at baseline would be predictive of non-remission in CHR subjects.

2. Method

2.1. Setting and participants

One hundred thirty-four help-seeking individuals fulfilling CHR criteria were enrolled from the prospective, naturalistic CHR cohort study in the Seoul Youth Clinic (Shim et al., 2008; Kwon et al., 2012). Study protocols and informed consent for the secondary data analysis were approved by the institutional review board of the Seoul National University Hospital; all participants signed written informed consent.

All CHR participants met at least one of the three established criteria for prodromal psychosis syndrome (Miller et al., 2002), which include the following: 1) attenuated positive symptoms (APS); 2) brief intermittent psychotic symptoms (BIPS); and 3) genetic risk with deterioration (GRD). Inclusion criteria for participation in this study were: 1) meeting the criteria for a prodromal psychosis syndrome, as stated above; 2) having ≥1 year of follow-up; 3) not having converted to full-blown psychosis according to the transition criteria on SIPS 3.1; and 4) the presence of full medical records, including the prescribed medications. Exclusion criteria were: 1) lifetime diagnosis of a psychotic illness, substance dependence, neurological disorder, 2) history of significant traumatic brain injury, 3) any significant medical condition that could manifest as a psychiatric condition, and 4) full-scale IQ < 70.

2.2. Data collection

Demographic and clinical data were obtained from the database of the cohort study at the Seoul Youth Clinic. CHR subjects received follow-up assessments every 6 months for 2 years. Assessments included the following measures: the severity of the prodromal symptoms, using the Structured Interview for Prodromal Syndromes version (SIPS) (Miller et al., 2002; Jung et al., 2010); depressive symptoms, using the Hamilton Depression Rating Scale (Hamilton, 1960); global functioning, using the Global Assessment of Functioning modified (GAF) (Hall, 1995); parental socioeconomic status (SES), using the Hollingshead scale (Hollingshead, 1975); handedness (Annett, 1967); family history of psychotic disorders, determined by the family interview for genetic studies (Gershon and Guroff, 1984); duration of untreated prodromal psychosis, obtained from interviews with the participants and their parents and medical record; and the intelligence quotient, using the Wechsler Adult Intelligence Scale (Yum et al., 1992), and the prescription data which is included: 1) the use of prescribed medication; 2) the mean chlorpromazine equivalent doses (Gardner et al., 2010); and 3) the medication possession ratio (Valenstein et al., 2002), calculated as the sum of the daily supply for all claims during a defined period of time, divided by the elapsed number of days during that period. The electronic medical records included data on whether the patients received the last prescribed medication, including gaps and refill information. In addition, medication compliance was assessed via clinical interviews with the patients and their families during all outpatient visits.

2.3. Statistical analysis

CHR participants were subdivided into those who were non-remitted both symptomatically and functionally during the past 12–24 months (CHR-NR) and those who remitted from CHR state within the past 12–24 months (CHR-R). Full remission criteria were defined as: 1) a score of ≥2 on all five positive SOPS symptoms (indicating absence of attenuated prodromal symptom criteria), and 2) a score >61 on the GAF scale (Emsley et al., 2011). Between-group comparisons of demographic, clinical, and prescription variables were performed using t-tests, chi-squared tests and the Mann–Whitney *U* test, as appropriate. We used Kaplan–Meier survival and log-rank test to determine the cumulative estimated rate of remission and to compare the two groups regarding time to combined symptomatic and functional remission as well as regarding time to symptomatic remission only. A linear mixed-effect model analysis was conducted to examine changes in clinical symptoms and functioning between the CHR-R and CHR-NR subjects over the 2-year follow-up. These models included possible confounding variables including age, sex and mean antipsychotics dosage during follow-up. Finally, we examined the predictive factors of time to remission by using multivariate Cox proportional hazard models. We conducted a multivariate Cox regression analysis by using forward and backward selection to identify the demographic and

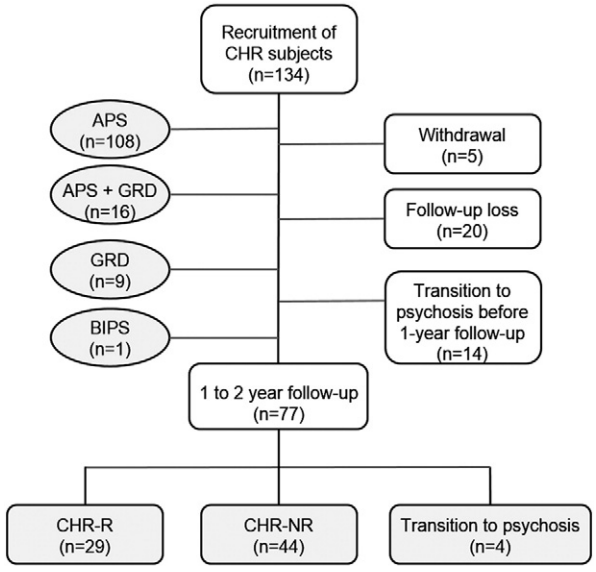

Fig. 1. Flow chart showing the selection process for the clinical high risk (CHR) for psychosis participants APS, attenuated positive symptoms; GRD, genetic risk with deterioration; BIPS, brief intermittent psychotic symptoms; CHR-R, CHR individuals who full remitted within a 2-year follow-up; CHR-NR, CHR individuals who did not full remit during the 2-year follow-up.

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