

CURRENT CONCEPT OF PRODROME FROM THE EXPERIENCE OF THE SEOUL YOUTH CLINIC HIGH RISK COHORT IN KOREA

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Abstract

The current criteria for identifying individuals at prodromal stage emerged from the need for early intervention in schizophrenia. Several clinical studies have shown that individuals at prodrome for developing psychosis can be identified using psychometric measures characterized by high reliability and predictive validity. Many studies on high-risk subjects have reported cognitive and functional deficits and biological abnormalities, especially in the fronto-temporal region. Longitudinal follow-up studies have also revealed that these biological abnormalities become more pronounced during the progression to psychosis. However, the use of these criteria also lead to the inclusion of heterogeneous individuals within the high-risk group insofar as the criteria may not exclude those experiencing the prodromal signs of mood disorders, such as bipolar disorder, or those with transitory subthreshold psychotic experiences. “Converters” and “non-converters” at the Seoul Youth Clinic have shown different clinical courses despite similar pharmacotherapy. Consideration of neurobiological factors and a combination of predictive markers might decrease the “false positive” problem. Further investigations will be conducted to identify predictive markers for psychosis. New criteria for identifying those at prodrome for schizophrenia in particular will present new opportunities for early intervention and research with respect to the prodromal symptoms of schizophrenia.

Key Words: schizophrenia, prodrome, high risk for psychosis

Declaration of interest: none

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Introduction

The onset of schizophrenia is preceded by a prodromal phase characterized by subthreshold psychotic symptoms, as well as a constellation of other clinical signs including cognitive deficits, negative symptoms, mood changes, and a decline in functioning (Cornblatt et al. 1999). Because schizophrenia is usually a chronic condition characterized by deteriorations in functioning over time, clinicians and researchers have attempted to identify individuals experiencing the initial stage of this disease. At first, the early psychosis movement focused on early recognition and treatment of first-episode psychosis in the hope of improving the long-term clinical and social outcomes of patients with schizophrenia.

Subsequently, clinicians and researchers have focused on identifying young people experiencing the putatively prodromal phase of schizophrenia and have examined whether intervention during this phase may result in ameliorating, delaying, or even preventing the onset of the full-blown disorder and thereby decrease the burden of disability or the incidence of psychotic disorders (McGorry et al. 2009). Operational diagnoses of high risk for psychosis have served as the foundations for numerous studies on the clinical prodromal stage and have been at the center of both research progress and limitations during the last decade. This article will discuss the issues related with the criteria for clinical high risk (CHR) and suggest future direction of these criteria derived from experiences at the Seoul Youth Clinic.

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The development of the current criteria for high risk

During the 1960s, long before the introduction of the CHR criteria, self-experienced deficits in patients with schizophrenia, or “basic symptoms,” were described by the German psychiatrist Gerd Huber and his colleagues. On the basis of long-term observations, they found that cognitive, affective, and social disturbances often emerged years before the first psychotic episode and that these early-stage changes were frequently not observable by others but were recognized only by the patients themselves (Yung et al. 2005). These symptoms were labeled “basic” because they were thought to most directly reflect the pathological somatic changes occurring during the course of psychosis (Schultze-Lutter et al. 2007). Basic symptoms seemed to be experienced even in the absence of positive symptoms, and thus it was assumed that individuals at increased risk for developing a psychotic disorder could be identified earlier in their prodromal phases by using this concept than by using the CHR criteria. The Personal Assessment and Crisis Evaluation (PACE) Clinic in Melbourne, Australia first utilized Bell’s suggestions for a “close-in” or “multiple gate screening” approach focused on psychologically troubled young people, a more clinically oriented approach than the traditional screening paradigm (Bell 1992). According to this ultra-high-risk (UHR) or CHR approach, age is the first risk factor defining UHR status: high-risk subjects are restricted to those aged 16–30 years because this period the risk for the onset of psychotic disorders reaches its peak during this period (Häfner et al. 1994). According to these criteria, individuals must also demonstrate at least one of the other risk factors: 1) attenuated psychotic symptoms, 2) brief, limited, intermittent psychotic symptoms (i.e., self-resolving psychotic symptoms), or 3) vulnerability (i.e., a trait-like factor such as schizotypal personality disorder or family history of a psychotic disorder in a first-degree relative plus a recent functional decline) (Phillips et al. 2005, Yung et al. 1996). The Comprehensive Assessment of At-Risk Mental States (CAARMS) was developed and validated by the PACE Clinic to identify these groups (Phillips et al. 2005). The Prevention through Risk Identification, Management, and Education (PRIME) prodromal research team at Yale University independently developed and validated another assessment tool, the Structured Interview for Prodromal States (SIPS) (Miller et al. 1999, Miller et al. 2002). Compared to the CAARMS, the SIPS seems to include a more restricted range of individuals (Miller et al. 2003).

Various approaches to identifying individuals at high risk are also based on different theoretical backgrounds and reflect different aspects of the deficits or abnormalities associated with risk. The UHR criteria, which are used in many centers around the world, seem to be directed at persons who are nearing the transition to psychosis, the so-called later phase of the prodromal period, whereas criteria addressing the basic symptoms seem to address those in the earlier phase of this period. Thus, these two sets of criteria have recently been combined in a number of studies focused on the

prodromal period (Häfner et al. 2004, Klosterkötter et al. 2005, Simon et al. 2004, Simon et al. 2006).

Clinical and neurobiological characteristics of the Seoul Youth Clinic high-risk cohort

The Seoul Youth Clinic

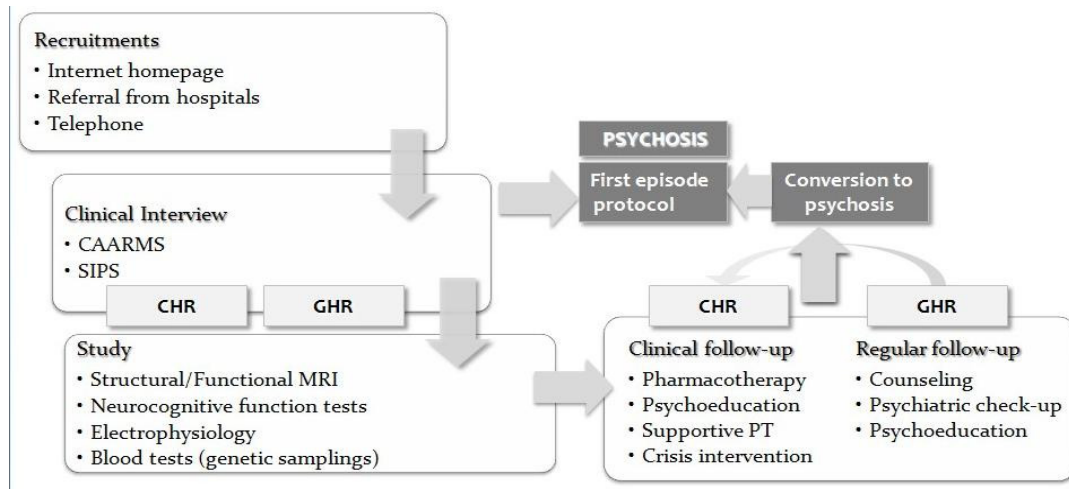
The Seoul Youth Clinic was established in Seoul, South Korea in November 2004 to provide early intervention and management services for young people at prodrome of psychosis and to identify biomarkers associated with the transition to psychosis. Young people at risk were divided into genetic and CHR subjects for purposes of monitoring. The CHR group is comprised of individuals who have sought psychiatric help for psychiatric symptoms such as depression, sleep disturbances, anxiety, social withdrawal, suspiciousness, deterioration in functioning, and reduced concentration and attention. CHR status was evaluated with two instruments, the CAARMS and the SIPS. Subjects meeting the criteria defined by either of these two instruments were enrolled in the study after providing informed consent. The age of participants was restricted to 15–35 years to increase the vulnerability of the sample to the development of psychosis.

Experienced psychiatrists assessed each subject’s eligibility for participation with an intensive clinical interview at intake. Clinician-rated scales and self-report questionnaires, neuropsychological tests including social cognitive tasks, and structural/functional neuroimaging were used at baseline and follow-up assessments (**Figure 1**). CHR subjects received follow-up assessments every 6 months and annually after enrollment. When a subject was judged to have progressed to psychosis, he or she was withdrawn from the CHR-related assessments and treated as a typical patient in the Seoul Youth Clinic program.

At intake, all CHR subjects were informed that they were at high risk for developing psychosis but that they would not necessarily develop a psychotic condition such as schizophrenia; they were told that about 40% of those at high risk transitioned to psychosis by the end of one year without any special treatment (Schultze-Lutter 2004, Yung et al. 2003). They were also informed that medications such as antipsychotics and antidepressants could help alleviate their putative prodromal symptoms despite potential side effects. After subjects and/or their legal guardians provided informed consent for medication, a large portion of CHR subjects was treated with medication and monitored carefully on a biweekly or monthly basis. CHR subjects were permitted to withdraw from CHR assessments at any time. Upon withdrawal from the study, they had the option of continuing the pharmacological interventions. Recently, we investigated the effectiveness and tolerability of atypical antipsychotic therapies in CHR subjects ($n = 27$) and found that low-dose antipsychotics were effective and safe in reducing prodromal symptoms (Shim et al. 2008b).

As of mid-August 2009, we had recruited 69 CHR subjects. Of these 69 CHR subjects, 61 met the criterion for (1) attenuated psychotic symptoms; one met the

Figure 1. Evaluation procedure for high-risk subjects in the Seoul Youth Clinic



CAARMS, Comprehensive Assessment of At-Risk Mental States; SIPS, Structured Interview for Prodromal Syndromes; CHR, clinical high-risk; GHR, genetic high-risk; PT, psychotherapy

criterion for (2) brief, limited, intermittent psychotic symptoms; and 13 met the criterion for (3) vulnerability; six subjects met criteria (1) and (3) concurrently. The criteria for subgroups (1)–(3) were based on standards previously developed by Yung et al. (2005) and McGlashan et al. (2003). The mean age of CHR subjects (42 males, 27 females) was 21.2 ± 4.0 years. Fifteen subjects (21.7%) were lost to follow up, and 13 of the remaining 54 subjects (18.8%) were identified during the mean follow-up period of 16.0 months as having converted to psychosis after participating in the study for a mean of 12.8 ± 11.0 months. The mean prodromal period for “converters” who converted to psychosis later (1.3 ± 1.1 years) was significantly shorter than was that for “non-converters” who did not convert to psychosis (2.4 ± 2.0 years) (p -value = 0.03). Most CHR subjects met criteria for the following comorbid diagnoses: depressive disorder ($n = 29$), anxiety disorder ($n = 14$), schizotypal personality disorder ($n = 8$), bipolar disorder ($n = 3$), adjustment disorder ($n = 1$), and avoidant personality disorder ($n = 1$). After the onset of psychotic symptoms, converters were diagnosed with schizophrenia ($n = 10$) or bipolar disorder ($n = 3$) according to DSM-IV criteria. We have been scheduling long-term follow-up appointments with this high-risk cohort to reveal the biological markers related to the progression to psychosis. Understanding the long-term clinical courses of non-converters will also help us in understanding the emergence of mild or brief psychotic symptoms in those without a psychotic disorder.

Clinical and neurobiological characteristics of CHR subjects

To understand the diagnostic status of the CHR

criteria, we must identify the precise features and prognoses of CHR subjects in the way that Kraepelin and Bleuler contributed to the understanding of schizophrenia by attempting to delineate its course and distinct features. At baseline, CHR subjects showed impaired social and affective functioning (Lee et al. 2008, Shim et al. 2008a), cognitive deficits in executive functioning and visuospatial memory, and social–cognitive deficits in theory-of-mind tasks (Chung et al. 2008). It was also demonstrated that the face-recognition skills of CHR individuals were inferior to those of normal controls, which would contribute to impaired social–cognitive abilities (Kim et al. 2010). These findings are in accordance with those of previous studies of high-risk individuals and can be interpreted as indicating that, although individuals at prodrome have milder psychotic symptoms than do patients with schizophrenia, their social, affective, and cognitive deficits may begin prior to the onset of psychosis and even progress to the level of schizophrenia after the onset of psychosis. However, patients with such other psychiatric conditions as mood and anxiety disorders can also show similar deficits in these multiple domains, and most patients with those diagnoses do not progress to psychosis. Thus, these findings must be augmented by longitudinal follow-up studies to provide reasonable evidence for changes specific to the progression to psychosis.

The clinical characteristics demonstrated by our CHR cohort thus far imply that the current criteria for high risk include heterogeneous subgroups: converters and non-converters. As previously noted, the converters in our CHR cohort had shorter prodromal periods as did the non-converters, but the two subgroups did not differ with respect to the severity of clinical symptoms at baseline. These findings demonstrate that converters

sought psychiatric help earlier than did non-converters due to the rapid worsening of their prodromal symptoms. This result indicates that the initial clinical courses of the two groups prior to the initiation of pharmacotherapy differed. We also found that the clinical courses remained different even after treatment with psychotropic drugs. The CHR group was treated with many kinds of psychotropic drugs, and the mean dosages were lower than were those used for the treatment of schizophrenia. The mean dosages of psychotropic drugs before the transition to psychosis and the baseline scores on the Brief Psychiatric Rating Scale (BPRS) of converters did not differ from those of non-converters. However, despite treatment with psychotropic drugs, converters showed a gradual increase in BPRS scores (Figure 2). This difference in the clinical courses of converters vs. non-converters and the low rate of transition to psychosis thus far (below 20%) strongly support the diagnostic heterogeneity of the CHR group (Haroun et al. 2006, Yung et al. 2008).

Neurobiological studies conducted on high-risk subjects have found midline neurodevelopmental abnormalities, such as abnormalities in the cavum septum pellucidum (Choi et al. 2008) and reduced cortical folding of the anterior cingulate cortex (Yucel et al. 2003), which resemble the anomalies observed in patients with schizophrenia (Kwon et al. 1998, Yucel et al. 2002). Because patients with other mental disorders, such as obsessive-compulsive disorder (Chon et al. 2009) and bipolar disorders (Fornito et al. 2007), are also characterized by such anomalies, it would appear that these abnormalities are indicative of vulnerability to a wide range psychiatric disorders rather than of vulnerability to psychosis in particular. CHR subjects in neurophysiological studies have also shown abnormalities in mismatch negativity resembling those observed in individuals with schizophrenia (Shin et al.

2009, Umbricht and Krljes 2005); these data are indicative of deficits in the early stage of auditory information processing. Although the abnormal mismatch negativity in chronic schizophrenia is a robust finding, neurophysiological abnormalities are also present in other psychiatric disorders (Hoening et al. 2005, Ogura et al. 1993). Thus, measurements of the longitudinal trajectories of this abnormality are also ongoing.

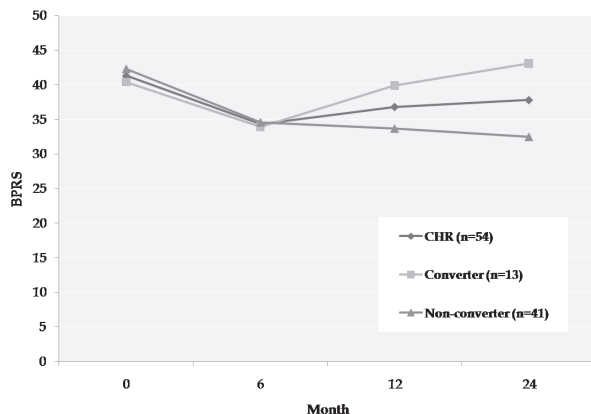
Drawing on this perspective, we recently performed a cross-sectional comparison of the cortical thickness of CHR subjects, schizophrenia patients, and normal controls (Jung et al. 2009). We found that the three groups differed significantly with respect to the cortical thickness of several regions and that the magnitude of the declines in these regions matched the stage of the illness (i.e., in order, normal controls, CHR subjects, and schizophrenia patients). The finding that cortical thinning progresses as psychosis develops is consistent with the concept that CHR subjects are young individuals experiencing a prodromal stage preceding the onset of psychosis. Indeed, longitudinal follow-up studies conducted by other CHR research teams have already revealed that the progressive cortical thinning in converters differed significantly from the trends observed in non-converters (Borgwardt et al. 2008, Pantelis et al. 2003, Takahashi et al. 2009). These studies assumed that progressive gray matter loss, especially in the fronto-temporal region, may precede the overt onset of psychotic disorders. On the other hand, these longitudinal studies also reinforce our assertion of heterogeneity in CHR subjects in view of differences in the neurobiological characteristics and clinical features of converters and non-converters.

Limitations and future directions in current CHR criteria

As noted above, data on clinical and research outcomes indicate that individuals identified by the current UHR criteria seem to be experiencing the prodromal phase of psychosis. CHR subjects resemble those with psychotic disorders, including schizophrenia, in terms of their clinical and biological characteristics, which supports the notion that current criteria for high risk address the prodromal phase of psychosis. Several controlled intervention trials including antipsychotics and cognitive therapy have shown promising results with respect to symptom reduction and prevention (or delay) of progression to psychosis in CHR subjects.

However, current CHR criteria (or concepts) face many challenges. Like other psychiatric diagnoses, current CHR criteria are also operational diagnoses based on clinical symptoms. Thus, they also suffer from the limitations inherent to a psychiatric diagnostic system. Because these criteria were designed to identify individuals who will progress to psychosis (or, in the narrow sense, schizophrenia), false-positive/-negative issues are inevitable, despite the emphasis on attenuated positive symptoms included in the criteria. As noted above, the most recent rates of transition from CHR status to full-blown psychosis (15%) (Haroun et al. 2006, Yung et al. 2008) were much lower than those initially reported (over 40%) (Yung et al. 2003).

Figure 2. Changes in BPRS^a scores according to the CHR^b subgroups



^aBPRS, Brief Psychiatric Rating Scale; ^bCHR, Clinical high-risk

Month: $F=10.9$; $df=3, 70.4$; $p<0.001$

Onset: $F=2.1$; $df=1, 59.4$; $p=0.156$

Month*onset: $F=4.0$; $df=3, 70.4$; $p=0.01$

Furthermore, in 2009 it was reported that the chance of recovering from CHR status was more than four times higher than that of converting to psychosis within one year (Simon and Umbricht 2009). This decline in the transition rate seems to have been precipitated by the earlier detection of individuals at prodrome or by the effectiveness of interventions (Yung et al. 2007). However, it is also possible that the putative prodromal symptoms of CHR subjects assessed by current diagnostic criteria are transitory and may not capture valid markers of vulnerability for developing psychosis.

Although current CHR criteria have the potential to provide a new way for understanding the development of schizophrenia and to prevent the overt onset of the disorder, the heterogeneous nature of the at-risk population remains a problem in need of a solution. Prodromal schizophrenia and other psychotic disorders, schizophrenia-spectrum disorders, and other relatively benign psychiatric disorders such as major depressive disorder can be classified according to CHR status under the current diagnostic system. This kind of diagnostic heterogeneity is also present among converters. For example, nearly one-fourth of the converters in the Seoul Youth Clinic have developed bipolar disorder with psychotic features, a plausible finding given that the initial prodromal phase for bipolar disorder cannot be clearly distinguished from that for schizophrenia (Correll et al. 2007, Thompson et al. 2003). These findings imply that the current symptom-based CHR criteria inevitably include heterogeneous individuals, a portion of whom may be experiencing phenomena unrelated to schizophrenia.

To overcome this limitation, the current CHR criteria should be modified to decrease the false-positive rate and to selectively address youth at risk for developing schizophrenia. To reduce the rate of false positives, the recent CHR criteria revised by the PACE clinic added a criterion to all the three UHR groups addressing impaired social and occupational functioning. The distinct clinical, cognitive (Brewer et al. 2006), and neurobiological characteristics of converters and non-converters present an opportunity for developing new criteria more specific to the prodromal phase of psychosis. Recently, a particular combination of clinical characteristics and cognitive deficits was reported as predicting conversion with high sensitivity and specificity (i.e., the combination of suspiciousness, anhedonia/social withdrawal, and reduced information-processing speed (Riecher-Rossler et al. 2009) or the combination of attenuated positive symptoms and verbal memory deficits (Lencz et al. 2006)). Despite the minimal number of converters in our data, studies at other sites (Brewer et al. 2005, Brewer et al. 2006) have provided consistent suggestions that baseline measurements of working memory, executive functioning, and verbal memory are potential candidates for inclusion in the new criteria. Neurobiological markers in the fronto-temporal region are also candidates for inclusion (Pantelis et al. 2009).

Although more specific neurobiological markers will be included in the criteria, the problem with false positives may continue. As evidenced by the issues with respect to schizophrenia and bipolar disorder, the current psychiatric diagnostic system based primarily on descriptions of psychopathology may not do justice

to the complexity of mental disorders and may raise fundamental questions about diagnostic status. Moreover, clinical utility would be improved by criteria that were inclusive rather than exclusive. The CHR concept should remain as a provisional diagnosis characterized by greater predictive power but limited by relatively high rates of false positives. Practical applications of the criteria should accompany careful consideration of all issues, including the problem of stigma.

Conclusions

The current CHR criteria, which were formulated with the aim of intervening early in the course of schizophrenia before the onset of psychosis, have enabled us to identify youth at prodrome for the development of this condition. However, the current diagnostic criteria produce a considerable number of false positives because a variety of psychiatric diagnoses (or conditions) other than prodromal schizophrenia meet the criteria for CHR status; this represents the major obstacle to early intervention in and relevant neurobiological research on schizophrenia. The CHR group seems to be composed of heterogeneous subgroups in terms of clinical and biological variables; classifying CHR subjects into converters and non-converters may be the schema that is most widely accepted by CHR researchers. The diagnostic entity associated with the CHR criteria remains in the development stage, which means that the status of CHR patients defined by the current CHR criteria is inevitably controversial. Future research should continue to update the diagnostic criteria used to identify vulnerability to schizophrenia.

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