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The Prodrome and Clinical Risk for Psychotic Disorders

Sandra M. Goulding, MPH, MA^{*}, Carrie W. Holtzman, MA, Hanan D. Trotman, PhD, Arthur T. Ryan, MA, Allison N. MacDonald, BA, Daniel I. Shapiro, MA, Joy L. Brasfield, BA, and Elaine F. Walker, PhD

Mental Health and Development Program, Department of Psychology, Emory University, 36 Eagle Row, Room 270, Atlanta, GA 30322, USA

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INTRODUCTION

Nature of the Problem

Despite decades of research on causes and treatment, schizophrenia and other psychotic disorders are still among the most severe and debilitating mental illnesses.¹ With typical onset in late adolescence/young adulthood, psychoses often have a chronic and relapsing course with potentially devastating functional implications. Although studies have examined the life span, research on the period preceding the modal age of psychosis onset has intensified.² Referred to as the prodrome, this period involves increasing symptoms and gradual functional decline that begin several months to years before clinical onset. As a result, the prodrome may offer the greatest promise for identifying neural mechanisms involved in the emergence of psychosis and implementing preventive intervention trials.³ This article provides an overview of (1) the manifestation and measurement of prodromal syndromes; (2) cognitive, environmental, and neurobiological factors associated with psychosis risk; and (3) diagnostic and treatments issues.

Definition

Although current diagnostic taxonomies draw boundaries among subtypes of psychotic disorders, accumulating findings suggest that (1) genetic risk factors are not specific to subtypes of psychosis and no single gene has a major impact on risk status,⁴ (2) prenatal and perinatal complications increase risk for affective and nonaffective psychoses,⁵ and (3) bioenvironmental risk factors (eg, substance abuse) are linked with risk for the full spectrum of psychoses.⁶ Although future research will likely result in the identification of distinct causal subtypes, at present the natural diagnostic boundaries are unknown. Therefore

psychoses and psychotic disorders are used in this article to refer to the spectrum of psychotic disorders, including affective and non-affective disorders.

Although the psychosis prodrome is a retrospective construct, with the term prodromal suggesting inevitability of subsequent illness, contemporary research on the prodrome is prospective in nature. Such studies use standardized measures to index subclinical perceptual, ideational, and behavioral symptoms of psychosis, and individuals whose symptoms exceed a specified severity threshold are designated as clinical high risk (CHR).^{7–10}

Prodromal Syndrome Criteria

Commonly used measures of CHR syndromes (Table 1) are based on empirical findings from retrospective research on symptoms and functional deficits that precede psychosis onset. Attenuated positive symptoms, pivotal in CHR criteria and indexed by all of these measures, include unusual perceptual experiences and ideations that do not meet the level of conviction and severity required for hallucinations and delusions. Likewise, the suspiciousness observed in the prodrome is not at the intensity of paranoid delusions, and the disorganized communication does not meet the threshold for diagnosis of a formal thought disorder. In addition to attenuated positive symptoms, measures also tap subclinical negative symptoms.

The Structured Interview for Prodromal Syndromes (SIPS) is the most widely used measure of prodromal syndromes in the United States. Like other measures that use standard CHR criteria, the SIPS enhances positive predictive power (ie, the ratio of true-positives to combined true-positives and false-positives) greater than the population prevalence rate for psychoses (ie, 1%–2%).⁹ Among those identified as putatively prodromal, only a proportion goes on to develop a psychotic disorder. Current estimates suggest that only 20% to 40% of those who meet CHR criteria convert to psychosis within 2 to 4 years. Therefore, although superior to predictive power based solely on genetic high risk (GHR; ie, family history of psychosis) status,¹¹ the rates of false-positives (ie, those who do not develop psychosis) identified by current measures of prodromal syndromes remain substantial. As a result, to improve predictive power, researchers continue to refine and combine these measures with other indices.

Nonetheless, as summarized later, CHR syndromes are associated with abnormalities similar to those observed in psychoses, with the most pronounced found in those who later convert to psychosis. These studies are typically longitudinal and involve both CHR and healthy control (HC) groups. In addition to monitoring progression of clinical, behavioral, and neurobiological factors assessed at baseline, follow-up assessments also track progression to psychosis onset. For example, the North American Prodrome Longitudinal Study (NAPLS¹²) uses the Structured Clinical Interview for Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition, axis I disorders to determine symptoms that indicate psychosis.¹³

CLINICAL FINDINGS

General and Social Cognitive Functioning

Cognitive deficits, particularly in memory and attentional functions, are among the most extensively documented aspects of psychosis.^{14,15} Likewise, a recent meta-analysis concluded that CHR individuals have significant cognitive deficits relative to matched HCs, and that CHR participants who convert to psychosis have greater baseline impairment than nonconverters.¹⁶ The severity of processing speed and verbal memory deficits also discriminates converters from nonconverters, with verbal memory impairment predicting faster conversion rates. In addition, cognitive impairments worsen over time, with those later in the developmental course of the prodrome displaying greater deficits in some domains than those in early phases.¹⁷

Considerable research has also shown pervasive social cognitive impairment, including deficits in social reasoning and processing of social and emotional information, in patients with chronic and first-episode psychosis (FEP).¹⁸ Current evidence suggests that CHR groups exhibit performance on social cognitive tasks that is intermediate to HC and FEP groups.¹⁹ Follow-up studies indicate that deficits are more pronounced in converters than nonconverters, and predict faster conversion rates even when controlling for general cognitive functioning at baseline.²⁰ In addition, evidence for temporal stability of impairment in those with recent onset of psychosis suggests that social cognitive deficits are traitlike rather than transient.²¹

Psychosocial Stress and Trauma

Although cross-sectional studies provide no consistent evidence that patients with psychosis experience more stressful life events (eg, death of loved one) than controls, longitudinal studies indicate that patients rate events as more stressful and have a significant increase in number of events before relapse.^{22,23} Further, studies of minor stressors (eg, being stuck in traffic) have linked these daily hassles with positive and affective symptom severity in patient groups.²³ Although the numbers of stressful life events/daily stressors do not differ between CHR and HC groups, those at CHR experience them as more stressful when they occur.²⁴ Within CHR groups, chronic stress is a predictor of positive and depressive symptom severity.²⁵ In addition, CHR and patient groups report more emotional reactivity to daily stressors, with daily stress intensifying symptom severity.^{26,27} Further, both groups also report greater exposure to childhood trauma, which has been linked with increased risk for psychosis conversion.²⁸ As discussed later, evidence also suggests greater biological sensitivity to stress in CHR groups.

Substance Abuse

Substance use, abuse, and dependence are common in patients with psychoses. CHR groups also show increased rates of substance use/abuse, and use of any illicit substance has been associated with increased risk of psychosis conversion.¹² Most research in the prodrome has focused on cannabis, which has been linked with increased risk of relapse and poorer clinical course in patient groups.²⁹ Interest in cannabis also stems from studies showing that administration of delta-9-tetrahydrocannabinol, the active ingredient in cannabis, can elicit

positive, negative, and cognitive symptoms of psychoses.³⁰ Retrospective studies of the general population have linked cannabis use with earlier onset of the prodrome and greater risk of psychosis.^{31,32} Although cannabis use is increased in CHR samples, prospective studies have not linked cannabis use and risk of psychosis conversion.³³ Further research is needed to determine whether use has a causal role in psychosis onset, or reflects self-medication of prodromal symptoms.

IMAGING

Neuroanatomy

A wide range of abnormalities in brain structure are associated with psychotic disorders. A recent review indicates decreases in intracranial and total brain volume, with the largest reductions in gray matter volume within cortical and subcortical regions.³⁴ White matter reduction has also been observed in both medication-naïve and medicated groups, and has been linked with severity of illness progression. A review of research involving CHR groups similarly indicates cortical and hippocampal gray matter volume reductions,³⁵ with more pronounced reductions in converters than non-converters.³⁶ Consistent with evidence of significant memory impairment, hippocampal volume seems to be reduced in patient and CHR groups.³⁷ Results suggest that brain volume reductions associated with psychosis precede illness onset. Further, increasing evidence of neuroplasticity in adolescents/young adults²² suggests that these developmental brain abnormalities may prove to be targets for preventive intervention.

Neurophysiology

Among the most consistently reported biomarkers in psychoses, as measured with electroencephalogram and electromyogram, are abnormal neurophysiologic indices that include measures of response inhibition and deviance detection.^{38–40} Measures of response inhibition include prepulse inhibition (PPI), P50 suppression, and antisaccade (AS) eye movement suppression. PPI is a reduction of the startle response that results when a startle stimulus is preceded by a nonstartling warning stimulus. In brief, PPI modulates the startle reflex, is associated with a smaller startle response, and enhances the ability to process stimuli. In contrast, P50 is a positive event-related potential (ERP), and decreases in P50 amplitude on presentation of repetitious stimuli reflect the ability to gate out redundant information. In addition, reflexive AS can be reduced by voluntarily focusing visual attention on a specific location or object. Errors and/or latencies indicate dysfunction in the frontal cortex, which controls saccadic eye movements.

With regard to deviance detection, measures include mismatch negativity (MMN) and P300 ERP. P300, a large positive component of the poststimulus ERP waveform, is more pronounced in response to novel stimuli and reflects capacity to attend to/detect a stimulus, update working memory, and attribute salience to a deviant stimulus. Reductions are associated with negative symptoms, declining attentional capacities, and gray matter volume deficits. However, MMN is a negative ERP waveform that is observed when repetitively alternating stimuli are periodically interrupted by a third distinctly different stimulus. Because MMN reflects greater capacity to detect differences among stimuli despite the

distractor stimulus (ie, auditory discrimination), reductions indicate sensory-memory anomalies.

Although comparisons of PPI in HC and CHR groups have not revealed consistent differences,^{41–43} few examine the association with psychosis conversion. There is more consistent evidence that CHR groups manifest reductions in P50 suppression relative to HCs,⁴⁴ with more pronounced reductions in those who also meet GHR criteria.⁴⁵ Likewise, comparisons of CHR and HC groups reveal trends for reduced AS suppression and MMN.^{46–49} However, the most consistent findings concern P300 amplitude. In brief, CHR groups manifest reduced amplitude relative to HCs and the magnitude of reduction discriminates converters from nonconverters.⁵⁰ P300 amplitude is also linked to white and gray matter volume,⁵¹ suggesting that functional brain impairments tapped by neurophysiologic indices reflect structural brain abnormalities.

PATHOLOGY

Neurotransmitters: Dopaminergic and Glutamatergic Systems

Theories of dopamine (DA) activity in psychosis have been prominent for decades, and substantial evidence indicates heightened DA in subcortical regions. Patients with psychosis manifest increased striatal DA activity and DA receptor density, and the extent of DA receptor occupancy (eg, D2 receptor) is associated with effectiveness of antipsychotics.⁵² Dysregulated presynaptic DA activity results in excessive DA release from areas projecting to the striatum, especially in the associative striatum where cognitive and limbic cortical inputs are integrated.⁵³ CHR groups also show heightened DA activity (eg, increased DA synthesis),^{54,55} with DA function in the brain stem recently linked to psychosis conversion.⁵⁶

Antagonists of the *N*-methyl-D-aspartic acid (NMDA) glutamate receptor increase extracellular glutamate, a known cause of oxidative stress, excitotoxicity, and hallucinations.⁵⁷ CHR and FEP groups have recently been shown to have increased levels of glutamate in the dorsal caudate.⁵⁸ In addition, expression of the proteins required for proper functioning of the glutamate system are reduced in patient, GHR, and CHR groups,⁵⁹ and evidence indicating an inverse relationship between thalamic glutamate levels and frontal cortical activity not found in HCs⁶⁰ suggests that aberrant glutamate activity alters cortical function in CHR individuals.

DA and glutamate systems in the brain are intimately linked functionally, and it is likely that both have a role in the cause of psychosis.⁶¹ In brief, negative symptoms and cognitive deficits are linked with glutamate dysfunction, whereas DA abnormalities are suggested to subserve positive symptoms. Interconnectedness of glutamate and DA systems also suggests that dysregulation in one can precipitate dysregulation in the other. Evidence of an inverse relationship between hippocampal glutamate and striatal DA activity in those at CHR but not HCs⁶² suggests that relatedness of hippocampal glutamate and striatal DA activity is altered. Results also indicated a link between DA uptake and severity of abnormal beliefs, and for the interaction of hippocampal glutamate and DA uptake to predict psychosis conversion.

Biological Stress Response: the Hypothalamic-Pituitary-Adrenal Axis

Because of the hypothesized role of stress in triggering symptom expression, indices of the biological stress response are of interest in CHR samples. The few studies that have investigated hypothalamic-pituitary-adrenal (HPA) function in CHR groups suggest increased baseline cortisol that also discriminates converters from nonconverters.^{63,64} Evidence suggests that converters have larger baseline pituitary volume than nonconverters, which also indicates increased HPA activity.⁶⁵ In addition, in a positron emission tomography study examining stress-induced cortisol and DA, those at CHR had more pronounced DA and cortisol responses than HCs, and increases in cortisol were positively associated with DA.⁶⁶ Results are consistent with the notion that stress exacerbates psychotic symptoms via augmentation of DA.

DIAGNOSTIC DILEMMAS

Significant controversies and challenges surround diagnoses of CHR syndromes.⁶⁷ With regard to inclusion of Attenuated Positive Syndrome (APS) as a formal diagnosis in diagnostic taxonomies, arguments in favor have included benefits for research and the observation that individuals who meet CHR syndrome criteria are typically seeking help and in distress. Arguments against involve concerns of overdiagnosis, stigmatization, and excessive medication of those who are false-positives. After considering proposals and preliminary data, it was decided that DSM-V will not include a provisional APS diagnosis.⁶⁸ Future research will decide whether APS is reconsidered for later DSM revisions, which will partly depend on enhancement of risk prediction beyond levels achieved with current measurement of CHR syndromes.

Meanwhile, practitioners are confronted with the need to diagnose CHR syndromes, and the range of nonspecific symptoms that tend to co-occur with the prodrome contributes to diagnostic complexity. A vignette of a typical CHR case is provided in Box 1.

Box 1

Clinical Vignette: CHR

John is an 18-year-old college freshman who arrived for the interview with a disheveled appearance. He reported no history of psychiatric problems, although he did see a counselor in high school for depressive feelings. John described current sadness and distress about increasing problems with concentration and academic performance. Although enthusiastic at the beginning of the school year, John has experienced a decrease in academic and social motivation and greater preoccupation with interpersonal relationships. He has made no friends in college, and thinks that the other students are avoiding him and criticizing him behind his back. Although not sure about the nature of the criticism, John speculated that it might be caused by his increased interest and involvement in paranormal phenomena. John stated that moving on campus at the start of freshman year and being exposed to a new peer group has resulted in him thinking that there may be paranormal influences at work in what he once would have considered coincidental interactions with others. During the first semester he joined a campus meditation group to deal with stress, and shared his fascination with paranormal

experiences with the members of the group. More specifically, John described his belief that most of what humans experience is through a sixth sense and that awareness of the sense is only achieved by a subgroup of individuals like him. Although he voluntarily admitted to the examiner that this could just be his imagination, John added that now, almost on a daily basis, he has transient feelings that he is receiving sixth-sense messages from others students when he passes by them on campus. Nonetheless, in hindsight, he thinks he should not have shared these ideas with the group, because it gave them the wrong impression.

Before prospective studies of CHR samples, retrospective studies documented the broad range of symptoms and syndromes (eg, depression, anxiety, obsessive-compulsive behavior, learning and attentional problems, personality disorders, and substance abuse) that precede psychosis. Prospective research in CHR samples yields similar findings, with many cases meeting criteria for at least 1 life-time/current diagnosis, and half having a life-time diagnosis of depressive or anxiety disorder.^{12,69} Thus, as with psychotic disorders, the psychosis prodrome is characterized by a high rate of comorbid psychiatric syndromes. In the absence of a formal diagnostic category, those with attenuated positive symptoms will continue to be diagnosed from typically co-occurring symptoms or syndromes.

Most of those meeting CHR criteria in research settings have been treated with psychotherapy or pharmacotherapy, with medications most commonly prescribed being antidepressants (49%), antipsychotics (24%), stimulants (14%), and mood stabilizers (11%).⁷⁰ Findings suggest that practitioners are treating mood syndromes and attenuated positive symptoms, but there are insufficient data to inform these interventions. For example, antipsychotics can reduce attenuated positive symptoms and delay psychosis onset, but there are no studies that show their effectiveness as preventive agents in CHR groups.⁷¹ Likewise, antidepressants may reduce symptom severity (especially pronounced depressive symptoms), but support for their effectiveness as preventive agents in CHR samples is lacking.

Although evidence suggests that cognitive behavioral interventions and omega-3 fatty acids can reduce attenuated positive and mood symptoms, more clinical trials addressing symptom reduction and psychosis prevention are needed.⁷¹ In the interim, there are 3 foci in CHR treatment. First, treatment should be designed to reduce current symptoms (eg, mood) that accompany CHR syndromes and cause significant distress. Second, treatment should augment protective factors (eg, improve family environment and social skills, and decrease substance use) to reduce the likelihood of psychosis conversion. Third, close monitoring increases the likelihood that positive symptoms will be rapidly and effectively treated if they reach psychotic threshold.

SUMMARY

Significant progress has been made in the characterization of CHR syndromes, and findings indicate that they are associated with milder versions of many psychological deficits and biological abnormalities observed in psychotic disorders. Moreover, those at CHR who manifest the most severe deficits and abnormalities seem to be at greatest risk for psychosis

conversion. Findings indicating prodromal changes in brain structure suggest that this stage is characterized by neuroplasticity that can provide leverage for preventive intervention. Although a level of scientific understanding that supports specific interventions has not yet been reached, the present trajectory of research progress holds promise for the future. One of the main goals of ongoing research is development of better prediction algorithms with the goal of attaining levels of positive predictive power that can justify delivery of preventive interventions in clinical trials.

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KEY POINTS

- Clinical high-risk (CHR) syndromes are associated with milder versions of psychological deficits and biological abnormalities observed in psychotic disorders, with those manifesting greater severity of deficits and abnormalities appearing to be at higher risk for conversion to psychosis.
- Evidence of changes in brain structure during the prodromal phase indicates a neuropathologic process that may be the focus of future preventive intervention efforts to target neural mechanisms involved in the emergence of psychosis.
- Justification for intervention efforts (ie, clinical trials) requires further empirical inquiry designed to enhance the predictive power of current algorithms used to identify individuals likely to develop a psychotic disorder.

Table 1
Measures of clinical high-risk symptoms/syndromes used in prospective investigations of CHR groups

Measure	Format		Symptoms/Syndromes Measured			
	Structured Interview	Clinical Checklist	Basic Symptoms ^a	Genetic Risk and Deterioration ^b	Brief Limited Psychotic Episode ^c	Attenuated Positive Symptoms ^d
BSIP	X		X		X	X
CAARMS	X		X	X		X
SIPS/SOPS	X		X	X	X	X
SPI-A/SPI-CY		X	X	X	X	X

Abbreviations: BSIP, Basel Screening Instrument for Psychosis⁷; CAARMS, Comprehensive Assessment of the At-risk Mental State⁸; SIPS/SOPS, Structured Interview for Prodromal Syndromes/Scale of Prodromal Symptoms⁹; SPI-A/SPI-CY, Schizophrenia Proneness Instrument, adult version/child and youth version.^{10,11}

^a Basic symptoms include cognitive-perceptive symptoms and cognitive disturbances.

^b Genetic risk deterioration generally involves genetic risk/family history of psychosis and functional decline.

^c Brief limited psychotic episode includes transient psychotic symptoms at a specified frequency over a given period of time.

^d Attenuated positive symptoms are subthresholds for the frequency, severity, and duration required for a psychotic episode/disorder.