Brief Communication

Creating a Platform to Bridge Service and Research for Early Psychosis

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Early identification of subjects at risk of developing psychosis is the key to early intervention. A prospective study on the psychopathological progress from prodromal state to full-blown psychosis was initiated in Taiwan in 2006. However, the clinical entity of our interests is ill-defined; therefore, recruitment of at risk subjects to participate in studies requires innovation. In November 2006, the study team launched a special clinic for cognitive and perceptual disturbance. In the first year, 142 subjects, mostly aged 16–30 year olds, made an appointment for this special clinic. More than 20 tentative diagnoses were made. Seventy-six subjects with a gradient of clinical severity were eligible for enrollment, and 68 gave informed consent to participate in the research. It seems that setting up a special clinic to provide a service for at risk subjects, combined with certain campaigns, could facilitate their engagement in a longitudinal prospective study for early psychosis.

Key Words: early diagnosis, prodrome, prospective study, schizophrenia, special clinic

Early intervention for first episode psychosis can lead to better prognosis.1 Intervention at the prodromal stage of schizophrenia might delay or even abort the onset of psychosis.2–4 In this regard, much effort has been invested worldwide during the past decade.5,6 Early identification of subjects at risk of developing psychosis is the key to early intervention.7 The phenomena that are frequently mentioned as heralding signals of schizophrenia are coined with the acronym “CASIS”,8 including cognitive deficits (subjective decline of intelligence, poor concentration, inefficient learning, rigid thinking); affective symptoms (inexplicable anxiety, atypical features of depression, fearfulness, obsession, hypochondriacal ideations); social isolation (having few close friends; withdrawn, distant, aloof, or isolated, frequent absence without identifiable causes); and school failure (marked deterioration of academic performance, or quitting school). As the prodromal symptoms of schizophrenia are usually nonspecific and the evolution of the clinical course might be intricate and protracted, early identification of schizophrenia is a challenging task.8,9

A prospective study on Psychopathological Progress of Early Schizophrenia-like Disorder (ESLD) (SOPRES), granted by the National Health Research Institute, was initiated in 2006, which...
comprised four related projects: clinical phenomenological follow-up study, neurobiological study, family genetic study, and awareness and pathways to help seeking study. Four psychopathological stages are going to be validated by SOPRES: very early stage (with some vague symptoms as described by CASIS, yet not fitting into common psychiatric diagnoses, or inexplicable by adjustment reactions); intermediate risk stage (with some odd appearance, behavior, speech, thoughts, or perceptual experiences); very high risk stage (with attenuated or brief intermittent psychotic symptoms); and first episode psychosis (FEP). These have been validated by a set of baseline and follow-up assessments, including neurobiological evaluations of event related potentials and magnetic resonance spectroscopy; neurocognitive evaluations of attention, memory, visual-motor function and intelligence quotient; as well as psychosocial evaluations. The Institutional Review Board of the study hospital has approved SOPRES.

The clinical entity of ESLD is ill-defined and the screening of at risk subjects in the general population is not feasible, therefore, recruitment of subjects to participate in the study requires innovative approaches. One example is the PACE (personal assessment and crisis evaluation) clinic that was established in 1994 by the Melbourne group as the first clinic specifically designed for adolescents who suspected with prodromal stage schizophrenia. Another example is the PRIME (prevention through risk identification, management and education) clinic that was started in New Haven in 1997 and extended to North Carolina, Toronto and Calgary in 1999. Both of these are two of the most important clinics in prospective studies of prodromal schizophrenia. We tried to adopt a multifaceted approach to schizophrenia research in community-based populations, which involved high school teachers, college and public counseling services, the high risk family (i.e. the family with schizophrenic patients), psychiatric clinics affiliated to the university hospital, and to general hospitals in metropolitan Taipei, website information, and mass media. In November 2006, a special clinic for cognitive and perceptual disturbance of adolescents and young adults was started to highlight our unique aim for screening assessment, counseling, and appropriate referrals.

In this report, we describe the demographics, clinical features, the proportion of subjects eligible to SOPRES among those who visited our special clinic, the proportion of these eligible subjects who participated in the study, types of pharmacotherapy given, and compliance with follow-up, to assess the feasibility of setting up a special clinic to provide a service for at risk individuals and to recruit subjects for research.

Methods

This was a naturalistic observation of subjects attending the special clinic for cognitive and perceptual disturbance of adolescents and young adults during November 2006 to October 2007.

Description of the special clinic

The special clinic ran regularly on Wednesday afternoons. It was attended by one general psychiatrist (Dr C.C. Liu, 1st and 2nd week of the month) and two child and adolescent psychiatrists (Dr Y.N. Chiu, 3rd week; and Dr M.C. Lai, 4th week). People who were suspected to be at risk of psychosis, (as perceived by themselves, their caregivers, primary psychiatrists, or counselors), could make an appointment by calling our research assistants or psychiatric outpatient nurse for an initial screening. To invite more subjects for assessment a low-threshold (presenting with CASIS or worrying if at risk of psychosis) was applied to invite more subjects for assessment. If the attendees who presented with CASIS were better classified as having other psychiatric disorders, such as organic brain syndrome, pervasive developmental disorder, social phobia, emotional disturbance, or even chronic psychosis, they were not eligible for the SOPRES. Each new attendee received a psychiatric diagnostic interview with the attending psychiatrist lasting at least 30 minutes. The first-contact psychiatrist referred the subject for interview by another psychiatrist if he or she had
difficulty with clinical judgment. If the subject were eligible for the SOPRES, he or she was asked for their informed consent to participate in our study after a thorough explanation. All subjects were advised about any type of pharmacological and/or psychosocial intervention, based on the empirical judgment of the attending psychiatrist, regardless of whether the subject was eligible for the SOPRES. The special clinic was intended to provide initial assessment rather than long-term follow-up, therefore, subjects generally visited once or twice and then engaged with regular clinical services if needed, although some of them opted to be followed up at our clinic for their convenience.

Assessment and clinical staging
The clinical impression was generally tentative rather than definitive and we excluded those who had a clear psychiatric diagnosis of another disorder. The attendees who were eligible for the SOPRES were evaluated by a set of clinical interviews that consisted of modified versions of latent schizophrenia scales, structured interview for schizotypy, and a scale of prodromal symptoms. The eligible subjects were categorized into different levels of clinical severity, with reference to the stage of risk in prodromal schizophrenia as follows:

1. Very early stage: subjects met CASIS indicators, but were unable to fit into any other diagnostic category.
2. Intermediate risk stage: subjects with some odd appearance, behavior, thinking (concrete, overabstracting, magic), feelings (inappropriate or incomprehensible expression of emotion), speech (circumstantial, stereotypical), or perceptual experiences (illusions or oversensitive to light or noise), not related to the severity of brief intermittent or attenuated psychotic symptoms.
3. Very high-risk stage: subjects with some brief intermittent or attenuated psychotic symptoms, such as unstable idea of reference, vague persecutory ideations, or transient hallucinations, which did not yet fit into FEP criteria.
4. FEP: full-blown psychotic symptoms that developed over the past year, which met the Diagnostic and Statistical Manual of Mental Disorders IV diagnostic criteria for schizophrenia, schizophreniform disorder, or schizoaffective disorder.

In terms of the risk of converting to full-blown psychosis, the predictability of staging was examined based on the clinical, neurobiological, neurocognitive, and psychosocial follow-up information, and reassessed annually.

Statistical analyses
The profile of our attendees was displayed by descriptive statistics and a few comparisons between differences in certain categorical variables were made by \( \chi^2 \) test. Three case vignettes are presented as illustrations to portray the psychopathological progress from prodrome to FEP.

Results
During the first year since November 2006, 142 individuals (76 male; average age: 20.8 ± 4.1 years; 73 aged < 21 years; Table 1) have made appointments for our special clinic in 43 sessions; 135 actually attended the clinic, 76 were eligible, and 68 of these (89%) signed their consent (Figure). Among the 68 participants, 15 (22%) did not agree to participate in the SOPRES until they had visited more than once. The tentative clinical impression of the 135 who visited the clinic comprised a wide range of psychiatric disorders, and the main diagnoses were roughly clustered into 20 categories (Table 2). Twenty-four of the 76 eligible participants were at the very early stage, 12 at the intermediate risk stage, 21 at the very high-risk stage, and 19 at FEP; only one, two, three and two subjects at each stage, respectively, declined to participate in the SOPRES. Significantly more subjects in the younger age group were not eligible (41 of 73 subjects aged < 21 years were ineligible vs. 25 of 69 aged ≥ 21 years; \( \chi^2 = 5.67, \text{df} = 1, p = 0.017 \)).

For eligible subjects, antipsychotic agents were prescribed to all subjects with FEP. Twenty of 21 very high-risk stage patients also received antipsychotics.
alone or together with antidepressants or anxiolytics/hypnotics: five were using low-dose sulpiride (≤200 mg/day), while the other 15 received second generation antipsychotics. Most of the intermediate-risk and the very early stage subjects were also empirically treated with antipsychotic agents (31/36), but the majority of these (22/31) only received low-dose sulpiride (≤200 mg/day) instead of second generation antipsychotics. More than half of them also received antidepressants and/or anxiolytics/hypnotics. Those who agreed to participate in the SOPRES were more likely to return to clinical services, as revealed by better compliance with scheduled visits (40 of the 68 recruited subjects complied with their appointment vs. 1 of the 8 declined subjects has returned to the clinic after initial assessment; $\chi^2 = 6.18, df = 1, p = 0.013$).

The three case illustrations revealed a range of psychopathology at each clinical stage. The wide variety of clinical symptoms demonstrated that clinical presentation in the very early and intermediate stages could mimic that of depression, or could be attributed to adjustment reactions, as...
Case illustration 1

A 17-year-old high-school student, who had been treated for depression since she refused to attend school 1 year ago, was referred to our special clinic by her primary psychiatrist for aggravated irritability, unexplainable fearfulness, ambivalence to her mother, and episodic temper tantrums over the past 2 months. She was tearful during the interview and had difficulty in finding the right words to describe how she felt. Idea of reference and vague persecutory ideation were detected but no formed delusion or hallucination was reported. She was admitted to our psychiatric ward for emotional instability and intermittent psychotic-like experiences under the impression of very high-risk prodromal stage of psychosis. She soon felt much better under treatment with 5 mg/day olanzapine, although she occasionally still felt insecure for no reason. However, she became emotionally unstable again soon after discharge, despite good treatment compliance. She needed her mother’s companionship at night for fear of something she could not identify. In the next month, she developed persecutory delusions toward her uncle and became extremely resentful towards him. Then, she believed that the players in a basketball game during a live television broadcast knew what she was thinking, and asserted that they were conspiring to utilize her for some illegal profit. A diagnosis of paranoid schizophrenia was ascertained at a later stage.

Case illustration 2

A 25-year-old man visited our regular psychiatric service for dysphoric mood, interpersonal oversensitivity, and some vague hallucination-like experiences. His primary psychiatrist treated him with 200 mg/day sulpiride and referred him to our special clinic for suspicion of very high-risk prodromal psychosis. However, he responded well to the medication within a short time. He showed no evidence of prodromal symptoms but poor coping with interpersonal interactions at his first visit to our special clinic. We advised him to try tapering off his medication gradually over the next 2 months and invited him to participate in our research. One year later, he was noted to be insomniac, irritable and suspicious. He repeatedly accused his girlfriend of testing him and thought that people on the street knew what he was thinking and that their eyes seemed to be giving him some messages. He did not take antipsychotic agents until 3 months later when he developed vivid auditory hallucinations with voices commenting and conversing, made actions, and was in turmoil. His psychotic symptoms improved greatly soon after he resumed antipsychotic treatment.

<table>
<thead>
<tr>
<th>Tentative diagnosis</th>
<th>n (%)</th>
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<tbody>
<tr>
<td>Very early stage of prodrome</td>
<td>24 (16.9)</td>
</tr>
<tr>
<td>Intermediate risk stage of prodrome</td>
<td>12 (8.5)</td>
</tr>
<tr>
<td>Very high risk stage of prodrome</td>
<td>21 (14.8)</td>
</tr>
<tr>
<td>FEP</td>
<td>19 (13.4)</td>
</tr>
<tr>
<td>Schizophrenia (non-FEP)</td>
<td>12 (8.5)</td>
</tr>
<tr>
<td>Bipolar disorder</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Organic brain syndrome</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Drug psychosis</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Neurotic depression</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Obsessive compulsive disorder</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Sleep disorder</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Anxiety disorder</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Eating disorder</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Social phobia</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Psychophysiological disorder</td>
<td>2 (1.4)</td>
</tr>
<tr>
<td>Stress reaction</td>
<td>4 (2.8)</td>
</tr>
<tr>
<td>Other neurotic disorder</td>
<td>7 (4.9)</td>
</tr>
<tr>
<td>Pervasive developmental disorder</td>
<td>3 (2.1)</td>
</tr>
<tr>
<td>Emotional disturbance</td>
<td>9 (6.3)</td>
</tr>
<tr>
<td>Mental retardation</td>
<td>1 (0.7)</td>
</tr>
<tr>
<td>Absent</td>
<td>7 (4.9)</td>
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FEP = First episode psychosis.
Case illustration 3
A 21-year-old college student reported that she was having problems studying at school. She attributed it to maladjustment because during the past year she had moved from a rural area to a city to study. She had strange perceptions of the outside world, and always tried to work out what was happening around her because everything felt unreal, and sometimes she felt something familiar although she had not experienced it before (déjà vu). Sometimes she became sentimental and moody, which was not necessarily related to any life event, and she was distracted by these negative feelings. She saw a psychiatrist and adjustment disorder was impressed by then. She felt relieved after suspended her schooling. She revealed that she had difficulty in distinguishing events in the real world from those depicted by fictional stories, and often became over-involved in the emotion aroused by stories that she read in books or watched on film. She could not concentrate on study after her recent return to school. This time, she became emotionally disturbed, and experienced vivid delusions of reference, persecutory delusions, and auditory hallucinations, and she had to leave school again.

Discussion
A special clinic for cognitive and perceptual disturbance can provide a service to people at risk for schizophrenia, and screen and invite subjects to participate in longitudinal follow-up studies. From our initial fieldwork on case recruitment, we found that the description of prodromal symptoms of schizophrenia was nonspecific and the concept of prodromal psychosis was unfamiliar to most people. Even mental health professionals were not ready to identify at risk subjects, especially when the validity of the four hypothetical clinical stages was pending verification by prospective studies. The lessons learned from our first year experiences are summarized below.

Recruitment of subjects with different levels of clinical severity necessitates a multifaceted approach that is tailored for each targeted subpopulation, as suggested by McGorry et al. Our special clinic offered an excellent window for referral because the 68 subjects represented more than two thirds of all SOPRES participants recruited during that period of time. The special clinic promoted our study, thus 89% of the eligible subjects agreed to participate in the SOPRES. For those who were hesitant to participate in the research, the special clinic facilitated recruitment by engaging with subjects from their initial visit. Fifteen of the 68 participants (22%) did not give their consent until they had visited the clinic more than once. For those who agreed to participate in our study, they were also more likely to receive follow-up services; thus, the connection formed with our research team was helpful in engaging them for further treatment, if necessary.

The nonspecificity of prodromal symptoms is still the biggest challenge for clinicians with regard to the wide variety of differential diagnoses. The younger age group (≤ 20 years old) seemed to have more difficulties recognizing whether their own problems were risk factors for psychosis, which is why we had two child and adolescent psychiatrists (YNC and MCL) in our team. The diversity of the attendees diagnoses also suggests a generally unmet need for mental health services. It is worth mentioning that 10% of the subjects were patients with schizophrenia who had already been treated by their primary psychiatrists for more than 1 year for symptoms similar to schizophrenia. This implies that some psychiatrists have difficulty in telling their patients about a diagnosis of schizophrenia; probably out of concern about stigmatization. The empirical pharmacotherapy that we delivered to prodromal subjects reflected the fact that, so far, no consensus can provide clinical guidelines for this clinical entity. Our results suggest that service and research could be mutually supportive. We wish to bring attention to subjects at risk of developing psychosis through establishment of our special clinic, as with the PACE and PRIME clinics, and hope that it continues to be a platform for investigation of prodromal schizophrenia and FEP in Taiwan.
Acknowledgments

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References