Cukurova Medical Journal
ÇUKUROVA ÜNİVERSİTESİ TIP FAKÜLTESİ DERGİSİ

Cukurova Med J 2016;41(3):437-446
DOI: 10.17826/cukmedj.234960

ARAŞTIRMA/RESEARCH

Retrospective evaluation of risk determinants in prodromal period with a group of schizophrenia patients

Bir grup şizofreni hastasında prodromal evrede risk belirteçlerinin retrospektif değerlendirilmesi

Soner Çakmak[1], Mahmut Onur Karaytuğ[1], Ufuk Bal[2], Lut Tamam[1], Ali Taşdemir[1]

[1]Cukurova University, Faculty of Medicine, Department of Psychiatry, Adana,Turkey.
[2]Askim Tufekci Hospital, Clinic of Psychiatry, Adana,Turkey.

Cukurova Medical Journal 2016;41(3):437-446.

Abstract

Purpose: This study aims to investigate the significance of risk determiners in the occurence of schizophrenia. and the link between the severity of determiners and the duration to full-blown schizophrenia.

Material and Methods: Patients older than 18 years old, diagnosed with schizophrenia are included in our study. SOPS (Scale of Prodromal Symptoms) is applied to determine the risk of schizophrenia prodromal period, scale scores are calculated and patients are classified in accordance to risk syndrome criteria defined in SIPS (Structured Interview for Prodromal Symptoms).

Results: Prodromal symptoms are detected in 68 of 100 patients. Of those 68 patients, 47 met the criteria for Attenuated Positive Prodromal Syndrome (APPS), 20 met the criteria for Brief Intermittent Psychotic Syndrome (BIPS), 24 met the criteria for Genetic Risk and Deterioration Syndrome (GRDS), 67 met the criteria for Psychotic Syndrome (PS), 44 met the criteria for Attenuated Psychosis Syndrome (APS) in DSM-5. Grandiosity, perceptual abnormalities/hallucinations, poverty of thought, deterioration in a role functioning, peculiar behaviour and appearance, decreased tolerance to normal stress are manifested to be meaningful in APPS,

Conclusion: It's clear that prodromal symptoms are increasing markedly the odds of psychosis and schizophrenia occurance in respect to normal population. Nevertheless, further customization and elaboration of risk determining criteria, searching and displaying neurobiological risk factors among criteria, will help to reliably identify risk groups and detect disorder in prodromal period.

Key words: Schizophrenia, risk factors, psikoz.

Öz

Amaç: Bu çalışmanın amacı şizofreni hastalarında prodromal evrede risk belirleyicilerin şizofreni gelişiminde anlamlılığını ve bu belirleyicilerin şiddeti ile şizofreni gelişme süresi arasındaki bağıntıyı araştırmaktır.

Gereç ve Yöntem: Çalışmaya şizofreni tanısı almış olan, 18 yaş üstü hastalar dahil edilmiştir. Şizofreni prodromal evre risk belirleyicisi olarak SOPS (Prodromal Sendromlar Ölçeği) uygulanmış, ölçek puanları hesaplanmış ve hastaların SIPS (Prodromal Sendromlar İçin Yapılandırılmış Görüşme)'e göre adlandırılan risk sendromları ölçütlerine göre sınıflandırması yapılmıştır.

Bulgular: Yüz hastanın 68'inde prodromal belirtiler saptanmıştır. 68 hastanın 47'si SIPS Hafif Pozitif Prodromal Sendrom (APPS), 20'si Kısa Aralıklı Psikotik Belirti Sendromu (BIPS), 24'ü Genetik Risk ve Yüksek Klinik Risk Kötüleşmesi (GRDS), 67'si Psikotik Sendrom (PS), 44'ü DSM-5 HPS ölçütlerini karşılamıştır. SOPS ölçek belirtilerinin anlamlılığına bakılmıştır. Ölçek belirtilerinden grandiozite, algısal anormallikler/varsanılar, düşünce fakirliği, bir rolün işlevinde kötüleşme, garip davranış ve görünüm, normal strese azalmış tolerans'ın APPS, BIPS ve DSM-5 HPS risk gruplarında anlamlı olarak bulunmuştur.

Sonuç: Prodromal belirtilerin psikoz ve şizofreni gelişme olasılığını normal populasyona göre belirgin oranda artırdığı açıktır. Ancak riskin belirleyici ölçütlerin daha özelleştirilmesi ve ayrıntılandırılması, ölçütlerde nörobiyolojik risk faktörlerinin de araştırılarak ortaya konulması risk gruplarının daha güvenilir şekilde belirlenmesine ve prodromal dönemde hastalığın tanınmasına yardımcı olacaktır.

Anahtar kelimeler: Şizofreni, risk faktörleri, psychosis

Yazışma Adresi/Address for Correspondence: Dr. Soner Çakmak, Cukurova University Faculty of Medicine, Department of Psychiatry, Adana, Turkey, E-Mail: drsoncak@hotmail.com
Geliş tarihi/Received: 06.12.2015 Kabul tarihi/Accepted: 07.02.2016

INTRODUCTION

Schizophrenia is a chronic brain disorder which is generally diagnosed in late puberty or early adulthood, and affects approximately 0.7% of the population. It is characterized by positive symptoms (delusions, hallucinations, and disorganized behavior), negative symptoms (low motivation, a reduction in social assertiveness and limited emotions) and cognitive symptoms (defects of perception)[1]. The most important deficit in the illness is in its early stages, and the progress of the disease is seen to be directly related to functionality before the onset of schizophrenia[2]. The existence of weak intellectual and psychosocial relations before the start of schizophrenia and other psychoses has been related to a worse and longer course[3-11]. For this reason, the need for studies to make early diagnosis and treatment easier in schizophrenia and other psychoses has become clear[12]. In this regard it is important to determine the prodromal symptoms and the risk of developing schizophrenia and other psychoses before they appear.

A period of mood changes, perceptual and functional disorders and social withdrawal are known to occur for weeks or years before the onset of the symptoms of psychotic disorders and schizophrenia[13]. Schizophrenia prodrome includes the time from when these non-specific symptoms and deficits appear to when symptoms of schizophrenia are seen. The symptoms observed in schizophrenia prodrome have helped in the diagnosis of psychosis risk syndromes. As the severity of the positive, negative, cognitive and motor symptoms is low and they do not last long, no comparison of psychotic or schizophrenia measurement has achieved this.

The history of studies on the identification of schizophrenia prodrome goes back more than a hundred years. However, reliable scales to diagnose 'psychosis risk syndromes' have only appeared in the past ten years. There are a number of scales to determine the existence or non-existence of the risk of developing psychosis or schizophrenia whose reliability and validity have been tested.

Among the widely used scales is the Bonn Scale for the Assessment of Basic Symptoms (BSABS), which is used to identify individuals who may become schizophrenic within an average of five years[14]. Comprehensive Assessment of at Risk Mental States (CAARMS)[15] and SIPS[16] show up delayed prodrome symptoms and in this way identify individuals in whom this will turn into schizophrenia[17].

The SIPS and CAARMS measures show that the risk of developing psychosis has increased by hundreds of times in the general population within a few years[17]. But at the same time, a significant proportion of those identified as having psychosis risk syndrome do not develop schizophrenia[18]. Only half of those developing psychotic disorders become schizophrenics[19]. SIPS was developed by Yung et al., remaining true to the Positive and Negative Syndrome Scale (PANSS) (Miller et al. 1999)[20]. This structured interview is used in the identification of high clinical risk or the lack of it, and indicates the severity of slight psychotic symptoms on a longitudinal plane.SIPS enables the diagnosis of three high clinical risk groups and one psychotic syndrome[21]; the diagnostic criteria of these risk groups and syndrome are summarized in Table 1.

Table 1. Prodromal risk groups & syndromes according to SIPS[22,23]

Syndromes/Groups	SIPS (Structured Interview for Prodromal Symptoms)
Attenuated Positive Prodromal Syndrome (APPS)	At least 1 positive symptom present in the attenuated range. Symptom started or worsened in the last year Occurs at least once per week over the past month.
Brief Intermittent Psychotic Symptom Syndrome (BIPS)	At least 1 positive symptom(s) present at psychotic threshold Symptom started within the last 3 months Occurs at least several minutes a day, at least once per month.
Genetic Risk and Deterioration CHR syndrome (GRDS)	A GAF score drop of at least 30% in the last month compared to 12 months ago Criteria for Schizotypal Personality Disorder are met, or client has a first degree relative with a psychotic disorder.
Psychotic Syndrome	A current or lifetime presence of psychotic symptom(s) Occur more than 1 hour a day for an average of 4 days a week.

SIPS: The Structured Interview for Prodromal Syndromes, GAF: Modified Global Assessment of Functioning Score (Endicott, Spitzer, Fleiss, & Cohen, 1976), CHR: Clinical High Risk.

In addition, as well as identifying these risk groups diagnosed according to SIPS, the risk of turning into psychosis under the names of Psychosis Risk Syndrome[24] or APS[25] has been added in DSM-5.

In the present study, we made a retrospective examination of the detailed symptomological histories of those who had been treated with a diagnosis of schizophrenia as in-patients at our clinic since 2012, from the first psychiatric complaints to the development of schizophrenia. We interpreted the symptoms according to SIPS and DSM-5, and in determining the risk of psychosis, we examined the correlation between the possibilities of true positives (development of schizophrenia in a patient where there was thought to be a risk syndrome) and false negatives (the development of schizophrenia in a patient where there was not thought to be a risk syndrome), the length of time to significance in the risk groups indicated by the SOPS scale and the onset age of schizophrenia and the prodromal phase, and the severity of prodromal symptoms as measured using the SOPS scale. It was the aim of the study to make a contribution to the literature on how much could be added to the predictability of the development of schizophrenia in schizophrenia patients showing the prodromal phase by psychosis risk syndromes indicated by SIPS and APS indicated by DSM-5.

MATERIAL AND METHODS

This study was conducted in conformity with the internationally accepted 1975 Helsinki Declaration as revised in 2002, the Turkish Health Ministry's 'Regulations on Drug Research' No 2148, dated 29 January 1993 and published in the Official Gazette and regulations published later. Ethical approval was obtained from Cukurova University Ethics Committee.

One hundred patients were included in the study. These were patients who were being treated as in-patients for schizophrenia at our 30-bed clinic between 2012 and 2015. Informed consent was obtained to use the medical records on the forms used on admission to the hospital for scientific purposes; the patients and their families were interviewed and details of the histories of their illness and treatment were taken.

Patients' histories of examination, diagnosis and admission to the clinic for treatment were recorded from information given by the patients, their families and those around them, symptoms were listed in reverse chronological order, and identification of patients' prodromal phase was shown by detailing symptoms in the period leading up to diagnosis. Patients were included in the study who were over the age of 18 and who had been diagnosed with schizophrenic disorder according to DSM-IV. Being under the age of 18 and having psychotic or non-psychotic diseases other than schizophrenia according to DSM-IV were exclusion criteria. Only patients hospitalized in our clinic and receiving treatment with a diagnosis of schizophrenia were included in the selection of patients, and those not hospitalized in our clinic and being monitored or treated as outpatients were excluded from the study.

Procedures

We identified the age of onset of schizophrenia of the 100 patients and separated them into those showing the prodromal phase and those not showing it by means of their detailed symptomatic histories. We compared these two groups to see if there was a significant correlation with the age of onset of schizophrenia.

In the second stage, we took the patients with prodromal phases and determined the age at which prodromal symptoms began the symptoms at this period and the duration of the prodromal phase. Then we detailed retrospectively the symptoms in the period up to the diagnosis of schizophrenia. We applied the SOPS scale for prodromal phase symptoms, and calculated the SOPS scores according to the degree of severity of the symptoms. We carried out an investigation to identify which clinical risk group (Table 1) criteria were carried by the patients according to SIPS in the prodromal phase before the diagnosis of schizophrenia. Also, we interpreted the APS criteria according to DSM-5 with patients' prodromal period symptoms, and looked at whether patients conformed to this diagnosis in the period up to when the diagnosis of schizophrenia was given. We compared the patient groups which met the criteria for each risk syndrome and DSM-5 APS with those who did not meet the syndrome criteria, and we looked at the significance of the SOPS scale symptoms for each of these risk syndromes.

In the final stage, we calculated the mean scores and standard deviations of schizophrenia onset age (SOA), prodromal phase period (PPP) and SOPS of

patients in the prodromal risk syndromes and DSM-5 APS groups. We checked the correlation in between the SOPS scores of each prodromal risk syndrome and DSM-V APS group and SOA and PPP.

Psychometric Tests

SIPS/SOPS: Diagnostic criteria relying on SIPS/SOPS allow the identification of people with a high risk of psychosis. They allow the correct prediction of psychotic episodes in the middle period. They are a suitable, valid and economical instrument for use by health organizations as a first step.

SOPS has four sub-scales and a total of 19 symptoms. A- Positive symptoms: 1- unusual thought content / delusional ideas; 2- suspicion / persecutory ideas; 3- grandiosity; 4- perceptive abnormalities / hallucinations; 5- disorganized communication. B- Negative symptoms: 1- social anhedonia or withdrawal; 2- avolition (apathy); 3- decreased expression of emotions; 4- decreased experience of emotions and self; 5- improverished thinking; 6- deterioration of role functioning. C- Disorganized symptoms: 1- odd appearance and behavior; 2- bizarre thinking; 3- attention and concentration problems; 4- personal hygiene and social skills. D- General symptoms: 1- sleep disorders; 2- dysphoric mood; 3- motor disorders; 4- decreased tolerance to normal stress. Symptoms are scored between 0 and 6: 0 = no symptom, and 6 = the highest level of severity. Total scores vary from 0 to 114. Its original name is Structured Interview of Prodromal Syndromes, and it was developed by Miller TJ et al[20].

DSM-5 APS: This is identified by the following criteria. A- The presence of at least one of the symptoms of delusion, hallucination, or disorganized speech at a low but appreciable level of severity, but no disorder in evaluation reality. B- The appearance of these symptoms at least once a week in the previous month. C- Starting in the previous year or deteriorating. D- This symptom creating distress and function disorder. E- Impossibility of explanation with another DSM-5 diagnosis. F- Never having had psychosis.

Statistical Analysis

All statistical evaluations in our study were carried out by means of the IBM Statistical Package for Social Sciences (SPSS) 20 (IBM Corporation, New York, United States) English language version. For comparison of the frequencies and rates of categoric variables, Chi-square, and where necessary Fisher's exact chi-square test, were applied. In comparing the means of the continuous variable of the two groups, Student T-test was used. The Pearson Correlation Test was used for the correlation of categoric variables.

RESULTS

Of the 100 patients included in the study, 53 were male and 47 were female. 32 patients (32%) had received a diagnosis of psychotic disorder on their first visit without showing a previous history of prodrome symptoms. 13 of these were male (24.5%) and 19 were female (40.4%). That is, 24.5% of the male schizophrenia patients in our study and 40.4% of the females had not shown a prodromal phase. These patients were assessed as having an acute psychotic attack on the first visit, but in time, as the disease progressed and became chronic, they were given a diagnosis of schizophrenia. In these patients, substances and other organic causes were excluded as possible causes of psychosis. Therefore, these patients were diagnosed with chronic schizophrenia, and categorized as a patient group not showing a prodromal phase, and because of this, SIPS was applied.

A prodromal phase was observed in 68 (68%) of the 100 patients. 28 of 47 female (59.6%) and 40 of 53 male (75.5%) patients had prodromal phase. Diagnosis was made according to the SIPS and DSM-5 of these patients. When patients who did or did not show a prodromal phase were compared by age of onset of schizophrenia, it was found that the age of onset of schizophrenia was significantly greater in those who showed a prodromal phase, independent of gender (Table 2). Looking at SOPS scores, age of onset of prodromal phase and duration of prodromal phase by gender, it was found that duration was longer in males, but that there was no clear difference between the sexes in terms of SOPS scores or age of onset (Table 3).

When patients with a prodromal phase were evaluated by psychosis risk syndromes and DSM-V APS, it was found that 47 (69.1%) met the criteria for SIPS APPS, 20 (29.4%) for BIPS, 24 (35.3%) for GRDS, 67 (98.5%) for PS, and 44 (64.7%) for DSM-5 APS (Table 3).

When age of onset of schizophrenia, duration of prodromal phase and SOPS scores were examined according to risk syndromes, no difference was seen in age of onset and total SOPS scores, but duration was found to be longest for GDRS and shortest for BIPS (Table 3).

Table-2. The correlation of schizophrenia onset age in patients with or without prodromal phase

	Age of onset (med±Sd)		
Gender(N)	**Prodromal phase(+)**	**Prodromal phase(-)**	**P**
Female(47)	(28)26.96±7.53	(19)24.74±6,79	0.3
Male(53)	(40)29.42±14.31	(13)21.31±5.37	0.05
Total(100)	(68) 28.4±11.98	(32)23.34±6.39	0.027

SIPS: Structured Interview of Prodromal Syndromes, SOA: Schizophrenia onset age, N: Number of patients, Med: Median, Sd: Standard deviation

Table-3: Schizophrenia onset age, prodromal phase period, prodromal phase onset age and SOPS average points in schizophrenia with prodromal phase, SIPS syndromes and DSM-V attenuated psychosis patients.

SIPS GROUPS AND SYNDROMES	Female(N=28) %	Male(N=40) %	Total(N=68) %
APPS	(20) 71.4	(27) 67.5	(47) 69.1
SOPS score (Med±Sd)			60.38±11.65
PPP(month) (Med±Sd)			73.38±81.86
SOA (Med±Sd)			28.6±10.8
BIPS	(7) 25	(13) 32.5	(20) 29.4
SOPS score (Med±Sd)			58.0±8,4
PPP(month) (Med±Sd)			62.4±153,1
SOA (Med±Sd)			28.45±14,8
GRDS	(12) 42.9	(12) 30	(24) 35.3
SOPS score (Med±Sd)			59.04±11.03
PPP(month) (Med±Sd)			91.6±149.72
SOA (Med±Sd)			28.9±12.96
PS	(28) 100	(39) 97.5	(67) 98.5
SOPS score (Med±Sd)			59.77±10.66
PPP(month) (Med±Sd)			70.7±106.73
SOA (Med±Sd)			28.09±11.77
DSM-V APS	(19) 67.9	(25) 62.5	(44) 64.7
SOPS score (Med±Sd)			60.7±11.86
PPP(month) (Med±Sd)			66.68±77.02
SOA (Med±Sd)			28.1±10.97
Schizophrenia with Prodromal Phase	(28) 100	(40) 100	(68) 100
SOPS score (Med±Sd)	55.82±11.2	62.15±9.73	59.54±10.75
PPOA (Med±Sd)	21.5±5.96	23.12±9.2	22.45±8.02
PPP(month) (Med±Sd)	60.21±67.94	76.47±126.77	69.78±106.2
SOA (Med±Sd)	26.96±7.53	29.42±14.31	28.4±11.98

SOPS: Scale of Prodromal Syndromes, SIPS: Structured Interview of Prodromal Syndromes, PPP: Prodromal phase period(month), SOA: Schizophrenia onset age, PPOA: Prodromal phase onset age, APPS: Attenuated Positive Prodromal Syndrome, BIPS: Brief Intermittent Psychotic Syndrome, GRDS: Genetic Risk and Deterioration Syndrome, PS: Psychotic Syndrome, APS: Attenuated Psychosis Syndrome, N: Number of patients. Med: Median, Sd: Standard deviation

Looking at the significance of SOPS scale symptom scores in risk syndromes in psychosis patients showing the prodromal stage, significance was found for APPS in thought content and delusional ideas, grandiosity, perceptual abnormalities, improverished thinking, deterioration of role functioning, strange behavior and appearance, and reduced tolerance to normal stress, for BIPS in grandiosity, perceptual abnormalities, improverished thinking, deterioration of role functioning and decreased tolerance to normal stress, and for DSM-5 APS in grandiosity, perceptual abnormalities, improverished thinking, deterioration of role functioning, odd appearance and behavior and decreased tolerance to normal stress against those without these symptoms, and it was concluded that these symptoms could be indicators of the development of schizophrenia (Table 4). A table is

not given for the GRDS group because significance was not found in the measurement symptoms. For PS, 67 out of the 68 cases met the criteria, and so the significance of symptoms was not investigated. When the connection of schizophrenia onset age and duration of prodromal phase to SOPS scores was investigated, no significant correlation was found (Table 5).

DISCUSSION

Even if the possibility of showing the risk of psychosis is high with scales with high dependability and validity in determining the presence or absence of the appearance of psychosis or schizophrenia, in fact it is seen that there is a greater probability of being able to predict the development of psychosis in comparing criteria according to the risk of development of psychosis in cases with positive criteria[27]. That is, it is seen that these tests are more accurate and reliable in the prediction of psychosis not developing in a person.

The proportion of those not showing a prodromal phase in schizophrenic psychoses is approximately 25%, because not all cases develop after a clear prodromal phase[28]. In our study this rate was 32% in the group as a whole, 40.4% in female schizophrenics and 24.5% in male schizophrenics. Yung conducted a study in 2006 on 292 subjects between the ages of 15 and 24 who either showed or did not show a prodromal phase, and found that psychosis developed in 13 of the patients who came with any kind of psychiatric complaint, and a prodromal phase was not seen in only one of the patients who developed psychosis. In a recent meta-analysis study, it was found that the rate of risk syndromes turning into psychosis was 22% in the first year, 29% in the second year, and 36% in the third year[29].

In a number of prospective studies, it was found that the proportion of change to schizophrenia of those with basic prodromal symptoms looking at BSABS was 70% over a period of ten years[14,15]. In contrast to these findings, it was established in a recent study on the general population that the proportion of change to psychosis in 3343 individuals with mild psychotic symptoms over a five year period was 1%[30]. In our study, schizophrenia developed in approximately 32% of patients without the appearance of a prodromal phase. When age of onset of schizophrenia was compared with whether or not patients showed a prodromal phase, it was found that patients who showed a prodromal phase had a significantly younger age of onset of schizophrenia independent of gender, and this result was expected. Patients showing slight psychotic symptoms which have not yet crystallized into a diagnosis of schizophrenia receive a diagnosis later in both genders in that they develop acute illness without showing a prodromal phase.

According to the data obtained in our study schizophrenia onset age were 23.34 ± 6.39 in those who did not show a prodromal phase and 28.4 ± 11.98 in those who did, and in those who showed a prodromal phase, prodromal phase onset age was 22.45 ± 8.02. These findings indicate that in patients in our study with SOPS criteria (+) there was a mean 69.78 ± 106.2-month prodromal phase from the onset age of the prodromal phase to the onset of schizophrenia, and they partially coincide with the view that SIPS, which is a structured interview for prodromal symptoms, shows up individuals in whom delayed prodromal symptoms turn into schizophrenia in one or two years[17].

The high value of the time period and the standard deviation in our study was partially the effect of the fact that six patients were diagnosed with schizophrenia approximately 20 years after the onset of prodromal symptoms. Considering gender, it was found that in SIPS (+) patients, the length of the prodromal phase was longer in males but there was no difference between genders in terms of SOPS scores and prodromal phase onset age.

In a scan of the literature, no study was found on the length of the prodromal phase in relation to gender in schizophrenic patients who had a prodromal phase. In our study, it was found that males showed a longer period of slight psychosis symptoms before being diagnosed with schizophrenia.

The PS group, which is among the risk syndromes identified by SIPS, has been found at a proportion of approximately 98.5% among psychoses which show a prodromal phase. In schizophrenias showing a prodromal phase, at least one psychotic symptom was found independent of the length of the prodromal phase which could not be ascribed to the diagnosis of schizophrenia or psychosis. One important detail is that DSM-5 APS cases were identified at the high rate of 64.7% in cases which

showed a prodromal phase, and this proportion showed 69.1% similarity to the APPS group, which is included among the SIPS risk syndromes. These values showed that the two characterizations could coincide with each other. Also, the fact that the two characterizations were seen together in 47 patients seen with APPS and 43 out of the 44 patients seen with DSM-5 APS supports this view.

Table-4: The significance of SOPS symptoms for APPS, BIPS and DSM-5 APS

SOPS SYMPTOMS	APPS			BIPS			DSM-V APS		
	Yes (N=47)	No (N=21)	p	Yes (N=20)	No (N=48)	p	Yes (N=44)	No (N=24)	p
	Med±Sd			Med±Sd			Med±Sd		
Positive Symptoms	14.8±5	16.1±3.4	0.3	16.4±3.1	14.7±5	0.15	14.5±5.1	16.6±3	0.07
Unusual thought content/delusional ideas	3.7±1.2	3.2±0.8	0.064	3.25±0.8	3.7±1.2	0.1	3.7±1.2	3.3±0.7	0.09
Suspicion/persecutory ideas	4±1.2	3.7±0.8	0.404	3.8±0.77	3.9±1.2	0.7	3.3±1.7	3.3±1.3	0.92
Grandiosity	1.5±2	2.7±1.6	0.016	2.8±1.6	1.5±2	0.01	1.2±1.9	3±1.5	<0.001
Perceptive abnormalities/hallucinations	2.3±2.1	3.3±1.3	0.046	3.3±1.3	2.3±2.1	0.05	2.2±2.1	3.3±1.2	0.026
Disorganized communication	3.4±1.3	3.2±1.3	0.53	3.3±1.3	3.4±1.3	0.87	3.5±1.3	3.1±1.2	0.32
Negative Symptoms	20.5±6	18±3.9	0.08	17.9±4	20.5±6	0.08	20.8±5.9	17.6±4	0.02
Social anhedonia or withdrawal	3.3±1.6	3.3±1.3	0.94	3.3±1.3	3.3±1.6	0.96	3.3±1.7	3.3±1.3	0.916
Avolition (apathy)	3.3±1.7	3.1±1.1	0.65	3.1±1.2	3.3±1.6	0.67	3.3±1.7	3.1±1.3	0.58
Decreased expression of emotions	3.2±1.4	3.1±1.2	0.74	3.1±1.3	3.2±1.4	0.76	3.3±1.4	3±1.2	0.54
Decreased experience of emotions and self	2.9±0.9	2.7±0.8	0.25	2.6±0.7	3±0.9	0.068	3±0.9	2.7±0.9	0.2
Improverished thinking	3.3±1.5	2.5±1.1	0.02	2.5±1.1	3.3±1.5	0.034	3.4±1.5	2.5±1.2	0.009
Deterioration of role functioning	4.4±1	3.3±1.4	<0.001	3.4±1.5	4.4±1	0.001	4.7±0.6	3±1.4	<0.001
Disorganization Symptoms	11.5±3.7	11.6±3.1	0.87	11.65±3	11.5±3.7	0.84	11.6±3.8	11.3±3	0.75
Odd appearance and behavior	3.9±1	3.3±1.2	0.043	3.4±1.1	3.8±1.1	0.102	4±1	3.1±1	0.001
Bizarre thinking	1.7±2.1	1.9±2	0.65	1.9±2	1.7±2.1	0.67	1.5±2	2.1±1.9	0.304
Attention and concentration problems	3.2±1.4	3.4±1	0.49	3.4±1	3.2±1.4	0.59	3.2±1.4	3.2±1	0.954
Personal hygiene/social skills	2.8±1.6	3±1.1	0.456	3±1.1	2.8±1.6	0.467	2.8±1.6	2.9±1	0.788
General Symptoms	13.6±4.3	12±3.6	0.13	12±3.6	13.6±4.2	0.166	13.8±4.3	11.9±3	0.064
Sleep disorders	3.2±1.6	2.7±1.6	0.228	2.7±1.6	3.3±1.6	0.17	3.2±1.7	2.8±1.5	0.297
Dysphoric mood	3.8±1.3	3.5±1.2	0.374	3.6±1.2	3.8±1.3	0.45	3.9±1.4	3.4±1.1	0.137
Motor disorders	2.3±1.5	2.4±1.2	0.727	2.6±1.1	2.3±1.5	0.428	2.2±1.5	2.5±1.2	0.384
Decreased tolerance to normal stress	4.3±1.2	3.3±1.2	0.003	3.3±1.2	4.3±1.1	0.003	4.4±1	3.1±1.1	<0.001
Total scores	60.4±12	57.7±8.3	0.28	58±8.4	60.2±11.6	0.449	60.7±11.8	57.4±8	0.222

APPS: Attenuated Positive Prodromal Syndrome, SOPS: Scale of Prodromal Syndromes, BIPS: Brief Intermittent Psychotic Syndrome, APS: Attenuated Psychosis Syndrome, N: Number of patients, Med: Median, Sd: Standard deviation

Table-5: The correlation of SOPS points with schizophrenia onset age and prodromal phase period

	SOA Med±Sd	SOPS Med±Sd	r	p	PPP(month) Med±Sd	SOPS Med±Sd	r	p
APPS(N=47)	28.6±10.8	60.4±11.7	-0.14	0.34	73.4±81.9	60.4±11.7	-0.06	0.68
BIPS(N=20)	28.5±14.8	58±8.4	0.06	0.82	62.4±153.1	58±8.4	0.22	0.36
GRDS(N=24)	29±13	59±11	-0.05	0.83	91.6±149.7	59±11	0.06	0.79
PS(N=67)	28.1±11.8	59.8±10.7	-0.03	0.8	70.7±106.7	59.8±10.7	0.03	0.82
DSM-V APS(N=44)	28.1±10.9	60.7±11.9	-0.14	0.38	66.7±77	60.7±11.9	-0.08	0.60
SIPS(+) (N=68)	28.4±12	59.5±10.8	-0.07	0.57	69.78±106.2	59.5±10.8	0.04	0.74

SOPS: Scale of Prodromal Syndromes, SIPS: Structured Interview of Prodromal Syndromes, PPP: Prodromal phase period (month) , SOA: Schizophrenia onset age, APPS: Attenuated Positive Prodromal Syndrome, BIPS: Brief Intermittent Psychotic Syndrome, GRDS: Genetic Risk and Deterioration Syndrome, PS: Psychotic Syndrome, APS: Attenuated Psychosis Syndrome, N: Number of patients, Med: Median, Sd: Standard deviation

At the same time, only two of the patients who had a prodromal phase met the PS criterion, and only one met the BIPS criterion. APPS, PS, and DSM-V APS criteria were met in 31 patients, APPS, GRDS, PS and DSM-V APS criteria in 12 patients, BIPS and PS criteria in eight patients, BIPS, GRDS and PS criteria in nine patients, BIPS, PS and DSM-V APS criteria in one patient, APPS, GRDS and PS criteria in three patients, and APPS and PS criteria in one patient.

The GRDS and BIPS risk groups, which have more specialized criteria, were found in a lower proportion in the study group. The fact that the criteria of the PS, APPS and DSM-5 APS groups consist of more general symptoms meant that the number of these groups in the study group was greater.

When examining the significance of SOPS scale symptoms, the PS group was not considered because 67 out of the 68 prodromal phase patients were in the PS risk group; and because no significance was found in any of the symptoms for GRDS, no table was given. However, in the APPS, BIPS and DSM-5 APS groups, the symptoms of grandiosity, perception abnormalities/hallucinations, improverished thinking, deterioration of role functioning, strange behavior and views, and reduced tolerance to normal stress were found to be significant in comparison with those which did not meet the criteria of these risk groups. In patients carrying a genetic characteristic (GRDS), these symptoms were not found to be significant. This showed that in patients carrying GRDS criteria, there was no significant difference from those not carrying criteria in the severity of SOPS symptoms.

When examining the patient groups which met the risk syndromes determined by SIPS, while an earlier prodromal onset and shorter prodromal phase was expected in GRDS positive patients who were thought to have a genetic predisposition, age of schizophrenia onset was found to be no different in GRDS patients in our study from others, and prodromal phase duration was longer than in other risk groups. This caused us to conclude that these genetic factors did not affect the age of onset of schizophrenia in prodromal stage patients and that it further increased the length of the prodromal phase.

One important result emerging from our study is the correlation between SOPS scale scores and schizophrenia onset age and length of prodromal phase. An increase or decrease in the SOPS score affects schizophrenia onset age and length of prodromal phase.

Finally, there is a later onset in schizophrenias which show a prodromal phase than in those which do not, and the lack of definite limits in prodromal risk criteria identified according to SIPS makes it more difficult to identify patients by means of these risk groups. However, assessment of prodromal phase symptoms with regard to risk by the use of the SOPS scale shows that schizophrenia can emerge an average of six years after the onset of prodromal symptoms. At the same time a connection was seen between SOPS scale scores and schizophrenia onset age and length of prodromal phase. It is clear that premorbid characteristics and prodromal symptoms together increase the likelihood of the development of psychosis and schizophrenia compared with the normal population. However, further specialization and detailing of the scales and elucidating the neurobiological risk factors by means of research will increase reliability in determining the risk.

The next step in research on this topic should be focused on the differences between schizophrenia

prodrome and the very high risk groups, and on preventing schizophrenia and at the same time helping to meet the needs of those in the very high risk groups. It is necessary to understand better the neurological basis of high risk syndrome and schizophrenia prodrome.

REFERENCES

1. Tandon R, Keshavan MS, Nasrallah HA. Schizophrenia, 'just the facts': what we know in 2008. part 1: overview. Schizophr Res. 2008;100:4-19.
2. Tandon R, Nasrallah HA, Keshavan MS. Schizophrenia, 'just the facts' 4. clinical features and conceptualization. Schizophr Res. 2009;110:1-23.
3. Gittelmqn-Klein R, Klein DF. Premorbid asocial adjustment and prognosis in schizophrenia. J Psychiatr Res. 1969;7:35-53.
4. Harrow M, Tucker GJ, Bromet E. Short-term prognosis of schizophrenic patients. Arch Gen Psychitry. 1969;21:195-202.
5. Bleuler M. The Schizophrenic Disorders: Long-Term Patient And Family Studies. New Haven, CT, Yale University Press. 1978.
6. Evans Jr, Goldstein MJ, Rodnick EH. Premorbid adjustment, paranoid diagnosis, and remission: acute schizophrenics treated in a community mental health center. Arch Gen Psychiatry. 1973;28:666-72.
7. Bromet E, Harrow M, Kasi S. Premorbid functioning and outcome in shizophrenics and non-schizophrenics. Arch Gen Psychiatry. 1974;30:203-7.
8. Strauss JS, Carpenter WT. The prediction of outcome in schizophrenia. I. relationships between predictor and outcome variables: a report from the WHO international pilot study of schizophrenia. Arch Gen Psychiatry. 1974;31:37-42.
9. Strauss JS, Carpenter WT. Prediction of outcome in schizophrenia: III. five year outcome and it's predictors. Arch Gen Psychiatry. 1977;34:159-63.
10. Bland RC, Orn H. 14-year outcome in early schizophrenia. Acta Psychiatr Scand. 1978;58:327-38.
11. Fenton WS, McGlashan TH. Prognostic scale for chronic schizophrenia. Schizophr Bull. 1987;13:277-84.
12. McGorry PD, Nelson B, Amminger GP, Bechdolf A, Francey SM, Berger G et al. Intervention in individuals at ultra-high risk for psychosis: a review and future directions. J Clin Psychiatry 2009;70:1206-12.
13. Sullivan SH. The onset of schizophrenia. Am J Psychiatry. 1927;6:105-34.
14. Gross G, Huber G, Klosterkotter J, Linz M. Bonn Scale for the Assessment of Basic Symptoms. Berlin, Germany, Springer, 1987.
15. Yung AR, Yuen HP, McGorry PD, Phillips LJ, Kelly D, Dell'Olio M et al. Mapping the onset of psychosis: the comprehensive assessment of at-risk mental states. Aust N Z J Psychiatry. 2005;39:964-71.
16. Miller TJ, McGlashan TH, Rosen JL, Cadenhead K, Cannon T, Ventura J et al. Prodromal assessment with the structured interview for prodromal syndromes and scale of prodromal symptoms: predictive validity, inter-rater reliability and training to reliability. Schizophr Bull. 2003;29:703-15.
17. Yung AR, Phillips LJ, Yuen HP, Francey SM, McFarlane CA, Hallgren M et al. Psychosis prediction: 12-month follow-up of a high-risk(prodromal) group. Schizophr Res. 2003;60:21-32.
18. Schlosser DA, Jacobson S, Chen Q, Sugar CA, Niendam TA, Li G et al. Recovery from at-risk state: clinical and functional outcomes of putatively prodromal youth who do not develop psychosis. Schizophr Bull. 2012;38:1225-33.
19. CannonTD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinalstudy in North America. Arch Gen Psychiatry. 2008;65:28-37.
20. Miller TJ., McGlashan TH., Woods SW., Stein K., Driesen N, Corcoran CM et al. Symptom assessment in schizophrenic prodromal states. Psychiatr Q. 1999;70:273-87.
21. Woods SW., Addington J, Cadenhead KS., Cannon, TD., Cornblatt BA., Heinssen R et al. Validity of the prodromal risk syndrome for first psychosis: findings from the North American Prodrome Longitudinal Study. Schizophr Bull. 2009;35:894-908.
22. Pearson R, Stuart B, Loewy R. The assessment of attenuated psychotic symptoms in adolescents: concepts, practical approaches and prediction of risk. UC San Francisco Previously Published Works, 2012.
23. Miller TJ, McQlashan TH, Rosen JL, Cadenhead K, Ventura J, McFarlane W et al. Prodromal assessment with the structured interview for prodromal syndromes and the scale of prodromal symptoms: predictive validity, interrater reliability, and training to reliability. Schizophr Bull. 2003;29:703-15.
24. Carpenter WT. Anticipating DSM-V: should psychosis risk become a diagnostic class? Schizophr Bull. 2009;35:841-43.
25. Carpenter WT, van Os J. Should attenuated psychosis syndrome be a DSM-V diagnosis? Am J Psychiatry. 2011;168:460-3.
26. American Psychiatric Association: Diagnostic and Statistical Manual of Mental Disorders, 5th Edition. Washington, DC, American Psychiatric Association, 2013.
27. Yung AR, Stanford C, Cosgrave E, Killackey E, Philips L, Nelson B et al. Testing the Ultra High Risk (prodromal criteria for the prediction of psychosis in a clinical sample of young people. Schizophr Res. 2006;84:57-66.

28. Hafner H, van der Heiden W. Epidemology of schizophrenia. Can J Psychiatry 1997;42:139-51.
29. Fusar-Poli P, Bonoldi I, Yung AR, Borgwardt S, Kempton MJ, Valmaggia L et al. Predicting psychosis: meta-analysis of transition outcomes in individuals at high clinical risk. Arch Gen Psychiatry. 2012;69:220–9.
30. Werbeloff N, Drukker M, Dohrenwend BP, Levav I, Yoffe R, van Os J et al. Self-reported attenuated psychotic symptoms as forerunners of severe mental disorders later in life. Arch Gen Psychiatry. 2012;69:467–75.
31. Cannon TD, Cadenhead K, Cornblatt B, Woods SW, Addington J, Walker E et al. Prediction of psychosis in youth at high clinical risk: a multisite longitudinalstudy in North America. Arch Gen Psychiatry. 2008;65:28-37.
32. Woods SW, Addington J, Cadenhead KS, Cannon TD, Cormblatt BA, Heinssen R et al. Validity of the prodromal risk syndrome for first psychosis: findings from the North American prodrome longitudinal study. Schizophr Bull. 2009;35:894-908.
33. Corcoran CM, First MB, Cornblatt B. The psychosis-risk syndrome and its proposed inclusion in the DSM-V. A risk-benefit analysis. Schizophr Res. 2010;120:16-22.