Prodromal Symptoms of Relapse in a Sample of Egyptian Schizophrenic Patients

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Background: Schizophrenic patients and family members often retrospectively report having observed a number of nonpsychotic symptoms and/or certain alterations in behavior that they believe preceded any psychotic symptoms and behavior. The identification of possible relapse before its actual occurrence and the timely intervention in management are expected to spare both patient and family the suffering and pain of a full schizophrenic episode. The aim of this study was to determine if prodromal symptoms could be used as valid predictors of relapse in schizophrenic disorders and the relative diagnostic values of these symptoms in a sample of Egyptian schizophrenic patients.

Method: One hundred Egyptian patients with schizophrenic disorders (DSM-III-R criteria) that had recently relapsed were retrospectively assessed for prodromal symptoms in the month preceding relapse. They were compared with 2 control groups, 50 Egyptian nonrelapsing schizophrenic patients and 50 healthy Egyptian individuals.

Results: Nonpsychotic symptoms were the most common prodromal symptoms occurring in relapsing patients. A significant difference in frequency of prodromal symptoms was found for relapsing patients versus nonrelapsing patients ($p < .001$) and healthy controls ($p < .05$). Prodromal symptoms appear to have a relatively specific value for predicting subsequent psychotic symptoms in those subjects who previously experienced such symptoms.

Conclusion: Clusters of nonspecific prodromal symptoms exist that significantly differentiate between relapsing, nonrelapsing, and healthy controls. Fine-tuning of the identification of these symptoms could be a plausible clinical tool to be used by psychiatrists and general practitioners alike to predict a possibility of an impending relapse.

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Relapse of schizophrenic disorders takes a toll on patients and their families and imposes a financial burden on hospitals and community resources.[1] Despite the great progress in treatment and prophylaxis of schizophrenic disorders in view of the introduction of neuroleptics and the use of psychosocial treatment, such treatment, which can spare affected individuals the suffering and consequences of relapse, is far from being fully utilized. The majority of patients (50%–75%) alternate between acute psychotic phases and phases of improvement or recovery.[2] Also, appraisal of prodromal symptoms is known to be important for early therapeutic intervention to prevent the development of full-blown psychotic episodes.[3] Moreover, studying early signs of relapse not only provides guidelines for initiation of medication for patients, but also helps psychiatrists to determine when medication dosages should be increased in patients already on maintenance therapy.[4]

The term *prodrome* is derived from the Greek word *prodromos* meaning "the forerunner of an event."[5] If the term *prodromal symptoms* is used with regard to schizophrenia, then the nature of these symptoms must differ from the specific or defining psychotic symptoms of schizophrenia. It would appear, therefore, to be more appropriate and less confusing to restrict the use of the term *prodromes* to nonpsychotic symptoms.[6] Also, it is worth mentioning that, as in clinical medicine, prodrome is a retrospective concept, diagnosed only after the development of definitive symptoms and signs.[7] However, the empirical investigation of prodromal symptoms in schizophrenia is a relatively recent development. The search of the literature revealed few scientifically based data regarding early signs of relapse or the length of the prodromal period. Birchwood et al.[8] observed that 75% of relatives noticed changes from 2 to 4 weeks before relapse, and Tarrier et al.[9] reported prodromal changes within 1 month of relapse in their prospective study. It was shown that patients and family members often retrospectively report having observed a number of nonpsychotic symptoms and/or certain alterations in behavior that they believe to have preceded the appearance of psychotic symptoms and behavior. The most frequently cited possible prodromal symptoms consist of mood changes, such

as tension, irritability, depression, anxiety, and withdrawal, and vegetative changes, such as disturbed sleep and loss of appetite.[4,10] However, some investigators have also included symptoms suggestive of early exacerbation of psychosis, such as hallucinations, inappropriate suspiciousness, and thought disorder.[11–13]

The aim of this study was to identify the nature of prodromal symptoms of relapse in a sample of Egyptian schizophrenic patients and determine if any of those symptoms could be used as valid predictors of relapse in schizophrenic disorders.

METHOD

Subjects

This retrospective study group consisted of recently relapsing Egyptian schizophrenic patients attending the outpatient clinics of the Institute of Psychiatry, Ain Shams University, Cairo, Egypt, over a period of 18 months. They were diagnosed using DSM-III-R criteria according to the patient version of the Structured Clinical Interview for DSM-III-R (SCID-P).[14] Patients excluded from the study included those diagnosed with schizophrenic disorders for the first time; those with a history or evidence of organic disorder of the central nervous system, significant habitual drug abuse, or alcoholism prior to the month of monitored prodromal symptoms or any clouding of schizophrenia diagnosis by past drug or alcohol abuse; those with schizoaffective disorders or mood disorders with psychotic features; and those with a history suggestive of any anxiety disorders or somatoform disorders. Relapse was operationally defined as "a return of symptoms satisfying the full syndrome criteria for an episode that occurs during the period of remission."[15(p852)]

Two control groups were selected. A group of 50 Egyptian patients with a schizophrenic disorder who had been in full remission for at least 6 months were selected from those attending the outpatient clinic of the Institute of Psychiatry, Ain Shams University. This group was meant to test the hypothesis that prodromal symptoms and/or symptom clusters occur mainly prior to relapse and do not occur in nonrelapsing patients (i.e., during remission). Full remission was operationally defined as a period during which an improvement of magnitude sufficient to consider the individual asymptomatic was observed (i.e., no longer meets the syndromal criteria for the disorder or has no more than minimal "residual" symptoms).[15]

In addition, a group of 50 healthy Egyptian individuals was selected from employees and workers at the Institute of Psychiatry, Ain Shams University, and their relatives to test the hypothesis that prodromal symptoms and/or symptom clusters do not occur in normal healthy persons (i.e., occurring as a part of normal reaction to stress).

Assessment

Assessment tools included the SCID-P, the nonpatient version of the SCID (SCID-NP),[16] and a semistructured interview based on the Arabic version of the Early Sign Questionnaire,[4] which was developed by a translation/retranslation process. The latter interview was designed for the detection of prodromal symptoms during the month preceding relapse. Herz and Melville[4] found that more than half of their patients had a relapse prodrome of less than 1 month with a median between 2 and 4 weeks.

Study Procedure

A pilot study with a senior colleague tested the interrater reliability of the interview based on the Arabic version of the Early Sign Questionnaire. The pilot sample consisted of 30 recently relapsing schizophrenic patients, selected from inpatients and outpatients at the Institute of Psychiatry, Ain Shams University, who were diagnosed according to the SCID-P. The overall interrater reliability of the Arabic version was very satisfactory ($\kappa = 0.88$).

For the study proper, written consent was obtained from all patients, their families, and the control subjects to participate. The 2 patient groups were assessed by the SCID-P and the semistructured interview based on the Early Sign Questionnaire. Family members of patients were interviewed by means of the interview based on the Early Sign Questionnaire. The control group was assessed by means of the SCID-NP as well as the Early Sign Questionnaire.

Statistical Analysis

Statistical analysis was carried out at the Public Health Department of the Faculty of Medicine, Ain Shams University, using the Microstat Package V-2 program for IBM. Descriptive statistics included measurement of mean, standard deviation, and range of minimum to maximum values. Analytic statistics included the Student t test to compare 2 independent parametric means (i.e., the mean age in the relapsing group vs. the mean age in the nonrelapsing group). Since some of the data were skewed, as proved by goodness-of-fit test, a statistical nonparametric method of data processing, the Wilcoxon rank sum test was used, which compared 2 independent medians. The Wilcoxon signed rank test was used to compare 2 nonparametric values in the same group (i.e., results obtained on the questionnaire for prodromal symptom assessment from patients and their relatives in the same group). Chi-square analysis was used to compare 2 different groups (i.e., qualitative data). The Cohen kappa was used to correct for chance agreement between 2 raters. Evaluation for diagnostic methods was done for sensitivity (the probability that a diseased subject shows a positive result), specificity (the probability that a nondiseased subject shows a negative result), positive predictive value (the probability to have the disease if the result of the test was positive),

Table 1. Sociodemographic Characteristics of Relapsing Patients, Nonrelapsing Patients, and Healthy Controls

Variable[a]	Relapsing Patients (N = 100)	Nonrelapsing Patients (N = 50)	Healthy Controls (N = 50)
Age, mean ± SD, y	29.02 ± 7.44	28.80 ± 11.80	29.76 ± 7.88
Gender			
Male	76 (76)	32 (64)	34 (68)
Female	24 (24)	18 (36)	16 (32)
Marital status			
Single	72 (72)	40 (80)	35 (70)
Married	26 (26)	9 (18)	13 (26)
Divorced	2 (2)	1 (2)	2 (4)
Children[b]	20 (71)	6 (60)	11 (73)
Educational level			
≤ 6 y	24 (24)	14 (28)	14 (28)
7–11 y	24 (24)	13 (26)	10 (20)
12 y (high school)	24 (24)	13 (26)	12 (24)
Part college	14 (14)	3 (6)	6 (12)
14 y	0 (0)	4 (8)	2 (4)
16 y	10 (10)	2 (4)	4 (8)
> 16 y	4 (4)	1 (2)	2 (4)
Employed	58 (58)	30 (60)	34 (68)
Residence			
Urban	76 (76)	43 (86)	36 (72)
Rural	24 (24)	7 (14)	14 (28)

[a]All values shown as N (%) unless otherwise specified.
[b]Percentage of married and divorced individuals within the group who have children.

Table 2. Clinical Characteristics of Study and Control Patient Groups

Variable	Patients (mean ± SD) Relapsing	Non-relapsing	t	p Value
Age at onset of schizophrenia, y	23.08 ± 6.21	23.00 ± 12.41	0.053	> .05
Age at first hospitalization, y	23.53 ± 5.12	21.46 ± 5.90	2.217	< .05
No. of hospitalizations	1.94 ± 2.57	1.10 ± 1.23	2.187	< .05
Total days in hospital	85.69 ± 94.02	42.28 ± 13.00	3.243	< .05
Months of noncompliance	10.55 ± 10.76	0.20 ± 0.61	6.785	< .001

and negative predictive value (the probability not to have the disease if the result of the test was negative).

RESULTS

Our study sample consisted of 100 relapsing schizophrenic patients. Single patients represented 72% of the group, while 26% were married and 2% were divorced. A total of 71% of the married or divorced patients had children. Educational levels were grade 6 or less (24%), grade 7 to 12 (24%), high school (24%), university (24%), and postgraduate levels (4%). Most of the patients (76%) were living in urban areas. Slightly more than half of the patients (58%) were employed, mostly in semiskilled or unskilled jobs (Table 1). Only 52% of the study sample were admitted to the hospital at the time of the study because their relapses were severe enough to require admission.

The disorganized type of schizophrenia was the most common diagnosis in both the study sample and the control patient group (66% vs. 70%), followed by the paranoid subtype (28% vs. 20%) and the undifferentiated subtype (6% vs. 10%). Four patients with the catatonic subtype (3 men and 1 woman) were excluded from the sample in view of their inability to cooperate in answering the required interviews. No statistically significant difference was found between the 2 patient groups regarding the distribution of the different types of schizophrenia among them.

Relapsing and nonrelapsing patients were not significantly different regarding age at onset of the first episode of schizophrenia, but the relapsing group had a significantly higher age at first hospitalization. Moreover, the relapsing group had a significantly greater number of hospitalizations as well as significantly longer duration of hospitalization. Relapsing patients had a significantly higher frequency and duration of noncompliance on medication prior to their assessment (Table 2).

Table 3 shows an overview of the prodromal symptoms as reported by relapsing patients, nonrelapsing patients, their respective relatives, and controls. Relapsing patients reported a significantly higher frequency of prodromal symptoms than did nonrelapsing patients ($p < .001$) and healthy controls ($p < .05$). Information drawn from relatives of relapsing patients and those of nonrelapsing patients and healthy controls confirmed the earlier finding. Relapsing patients and their relatives generally seemed to agree on the nature of symptoms preceding their relapse (Table 4). Our findings revealed that nonpsychotic symptoms were the most common prodromal symptoms as reported by both the relapsing patients and their relatives.

When we consider the presence of the 29 symptoms of the questionnaire based on the Early Sign Questionnaire in the relapsing patients compared with the nonrelapsing patients and the healthy controls, the sensitivity of the questionnaire is 0%, as is the positive predictive value. However, the negative predictive value and test accuracy is 16.67% when relapsing patients are compared with the nonrelapsing group, and both are 33.33% when compared with healthy controls, but specificity is 100% in all conditions (Table 5). For the individual prodromal symptoms, sensitivity ranged from 2% to 72%; specificity, from 36% to 100%; positive predictive value, from 52.38% to 100%; negative predictive value, from 25% to 59.52%; and test accuracy, from 34.67% to 77.33%.

Multiple comparisons were done to improve sensitivity, positive predictive value, and test accuracy (efficiency) of the questionnaire. Table 6 demonstrates 5 suggestions of the smallest number of symptoms that could be used to draw attention to the possibility of a relapse.

Table 3. Frequencies (%) of Prodromal Symptoms According to the Questionnaire in the Different Study Groups[a]

Symptom	Relapsing Patients (N = 100) [A]	Nonrelapsing Patients (N = 50) [B]	Relatives of Relapsing Patients (N = 100) [C]	Relatives of Nonrelapsing Patients (N = 50) [D]	Healthy Controls (N = 100) [E]	Chi-Square Values [A] vs. [B]	[C] vs. [D]	[A] vs. [E]	[C] vs. [E]	[B] vs. [E]	[D] vs. [E]
Tense and nervous	60	32	72	38	64	10.455*	16.148**	0.225	1.003	10.256**	6.763*
Eating less	52	40	50	40	48	1.923	1.339	0.213	0.053	0.649	0.649
Trouble concentrating	64	40	64	40	40	7.792*	7.792*	7.792*	7.792*	0.000	0.000
Trouble sleeping	58	6	66	6	44	37.355**	48.309**	2.625	6.653*	19.253**	19.253**
Enjoy things less	54	30	54	36	40	7.729*	4.327*	2.614	2.614	1.099	0.170
Restlessness	58	48	50	32	28	1.345	4.383*	21.019**	6.595*	4.245*	0.191
Can't remember things	44	50	42	40	20	0.483	0.055	8.333*	7.123*	9.890*	4.762*
Depression	64	30	68	30	52	15.457**	19.475**	2.000	3.647	5.002*	5.002*
Preoccupied with 1 or 2 things	34	10	38	18	56	9.979*	6.197*	6.653*	4.383*	23.926**	15.487**
Seeing friends less	34	0	26	6	28	21.983**	8.549*	0.551	0.068	16.279**	8.576*
Am being laughed at, talked about	50	26	44	0	4	7.882*	31.132**	31.142**	25.084**	9.490*	2.041
Loss of interest in things	38	0	50	0	24	25.446**	37.500**	2.940	9.293*	13.636**	13.636**
More religious thinking	24	0	24	0	24	14.286**	14.286**	0	0	13.636**	13.636**
Feeling bad for no reason	24	16	20	0	24	1.271	11.538**	0	0.318	1.000	13.636**
Feeling too excited	44	6	30	0	32	22.371**	18.750**	2.000	0.063	10.981**	19.048**
Hearing voices, seeing things	28	8	22	8	0	7.945*	4.560*	17.213**	21.891**	4.167*	4.167*
Feeling worthless	22	40	26	10	12	5.357*	5.205*	2.196	3.893*	10.187**	0.102
Talking in a nonsense way	34	4	42	4	0	16.447**	23.220**	21.983**	29.167**	2.041	2.041
Believe someone else is controlling	20	8	14	8	0	3.571	1.136	11.538**	7.721*	4.167*	4.167*
Bad dreams	36	28	24	20	28	0.960	0.304	0.960	0.282	0.000	0.877
Too aggressive	20	0	22	0	8	11.538**	12.891**	3.571	4.560*	4.167*	4.167*
Feeling angry at little things	48	12	42	18	32	18.750**	8.556*	3.488	1.406	5.828*	2.613
Not caring about way I look	32	22	46	28	36	1.630	4.500*	0.240	1.363	2.380	0.735
Having trouble with spouse, mate	38	8	38	8	24	14.881**	14.881**	2.940	2.940	4.762*	4.762*
Thoughts of hurting, killing self	24	16	18	10	8	1.271	1.643	5.621*	2.663	1.515	0.122
Frequent aches, pains	26	40	24	32	20	3.073	1.09	0.658	0.304	4.762*	1.871
Fear of "going crazy"	26	40	14	10	16	3.073	0.482	1.902	0.107	7.143*	0.796
Thoughts of hurting, killing others	28	6	12	0	12	9.840*	6.522*	4.868*	0.000	1.099	6.383
Drinking more, using drugs	2	0	2	0	0	1.014	1.014	1.014	1.014	...	...

[a]Questionnaire based on the Early Sign Questionnaire.
*p < .05.
**p < .001.

Table 4. Comparison Between Groups Using the Questionnaire[a]

Comparison	ESQ Score (Mean ± SD)	Z (of t Test)	p Value
Relapsing patients vs nonrelapsing patients	37.45 ± 15.54 vs 19.52 ± 16.47	6.193	< .001
Relatives of relapsing patients vs relatives of nonrelapsing patients	36.0 ± 18.45 vs 15.24 ± 14.84	6.780	< .001
Relapsing patients vs healthy controls	37.45 ± 15.54 vs 24.96 ± 17.72	2.644	< .05
Relatives of relapsing patients vs healthy controls	36.0 ± 18.45 vs 24.96 ± 17.72	2.074	< .05
Healthy controls vs nonrelapsing patients	24.96 ± 17.72 vs 19.52 ± 16.47	1.59	> .05

[a]Questionnaire based on the Early Sign Questionnaire.

Table 5. Diagnostic Values (%) for the Questionnaire in Relapsing Patients Compared With Nonrelapsing Patients and Healthy Controls[a]

Diagnostic Value	Compared With Nonrelapsers	Compared With Healthy Controls
Sensitivity	0	0
Specificity	100	100
Positive predictive value	0	0
Negative predictive value	16.67	33.33
Test accuracy	16.67	33.33

[a]Questionnaire based on the Early Sign Questionnaire.

Table 6. The Smallest Number of Symptoms That Can Give the Best Diagnostic Values

Suggestion	Value: Sensitivity	Specificity	Positive Predictive	Negative Predictive
1. At least 2 of the following: Restlessness; Am being laughed at, talked about; Hears voices, sees things; Talking nonsense; Believe someone else is controlling	64	96	97	57
2. At least 1 of the following: Am being laughed at, talked about; Hears voices, sees things; Talking nonsense	70	96	98	62
3. At least 4 of the following: Tense and nervous; Trouble sleeping; Depression; Seeing friends less; Loss of interest in things; Feeling too excited; Talking nonsense; Feeling angry at little things; Having trouble with spouse, mate	56	90	97	29
4. At least 4 of the following: Trouble concentrating; Trouble sleeping; Restlessness; Can't remember things; Depression; Am being laughed at, talked about; Loss of interest; Hears voices, sees things; Talking nonsense	62	92	94	55
5. At least 4 of the following: Tense and nervous; Eating less; Trouble concentrating; Trouble sleeping; Enjoy things less; Restlessness; Depression; Am being laughed at, talked about	64	70	91	28

DISCUSSION

The present study was specifically designed to investigate the possibility of identifying a cluster of prodromal symptoms that could predict relapse of schizophrenia in Egyptian patients. A highly significant difference ($p < .001$) was found in the presence of prodromal symptoms in relapsing patients compared with nonrelapsing patients, which may indicate that prodromal symptoms occur mainly prior to relapse and not during remission. Also, a significant difference ($p < .05$) was found in the presence of prodromal symptoms in relapsing patients compared with healthy controls, suggesting that prodromal symptoms occur mainly prior to relapse and do not occur as a part of normal reaction to daily stress.

Our results were in accordance with those of previous studies in that a number of nonpsychotic symptoms and behavioral changes were prodromal to the onset of elevation of psychotic symptoms in the course of schizophrenia. The onset of psychosis should therefore not be considered as an "all-or-none" phenomenon. It is much more likely to be a gradual process involving a progression from subtle disruption in perception of reality and thought structure to more blatant inability to identify reality or think coherently.[13] Earlier reports[17–19] suggest that, if careful observations are made, gradual increases in psychiatric symptoms can be observed.

In many cases, the supposedly prodromal symptoms may reflect difficulty of the individual in coping with initial stages of psychosis, but the nonpsychotic symptoms may be more apparent than the more subtle, and perhaps more private, psychotic ones.[20] Thus, many relapses are preceded by the appearance of prodromal symptoms and behaviors, which may last from few days to a few weeks or more. The presence of prodromal symptoms often does not predict impending relapse since the probability of progression to relapse depends on the complex interaction of many personal and environmental factors, including the availability of prompt and effective psychiatric intervention.[21]

The most common prodromal symptoms reported by patients and their relatives in the present study were non-

psychotic in nature, involving trouble concentrating, depression, being tense and nervous, trouble sleeping, restlessness, enjoying things less, and eating less. This finding is similar to those found in many previous studies.[4,7,9–13,17,19,20,22–26] However, these symptoms were also experienced by some of the nonrelapsing patients, but at a lower frequency, indicating a possible difference in coping strategies between relapsers and nonrelapsers. Also, the same symptoms were experienced by healthy controls, indicating that those symptoms may not be specifically prodromal. This finding in earlier studies has led some authors to include some psychotic symptoms in the description of the prodromal stage of schizophrenic patients.[11–13] This inclusion may compromise the original objective of predicting the occurrence of psychotic symptoms before they actually take place. We believe that our results support the notion that, within the clinical community of schizophrenic patients, certain nonpsychotic symptoms could be used as significant predictors to possible relapse. However, all early warning signs, including prodromal symptoms, mild psychotic symptoms, and certain behaviors, should be included as well.

Prodromal symptoms are obviously ambiguous in their diagnostic values. In our study, a broad range of values was found for sensitivity, specificity, positive and negative predictive value, and test accuracy. This is consistent with the ambiguity found in previous studies, which found sensitivity values ranging from 50% to 73% and specificity values ranging from 16% to 100%.[8,9,24,25] Also, Gaebel et al.[27] found that specificity was relatively high, ranging from 70.4% to 93%, while sensitivity was considerably low, ranging from 7.7% to 14.4%. The positive predictive value was also low, ranging from 15.3% to 42.9%, while the negative predictive value ranged from 67% to 73.9%.[27]

The high specificity reported by this and other studies may indicate that a substantial increase in prodromal symptoms not followed by a substantial increase in psychotic symptoms is relatively rare. On the other hand, the comparatively low sensitivity indicates that many increases in psychotic symptoms are not preceded by increases in putative prodromal symptoms. In other words, prodromal symptoms do appear to have a specific value for subsequent psychotic symptoms in those subjects who experience such prodromal symptoms.

A comparison between results (on the interview based on the Early Sign Questionnaire obtained from both patients and their relatives) in the present study and those obtained in the original study by Herz and Melville[4] in Atlanta, Ga., and Buffalo, N.Y., using Wilcoxon rank sum test reveals a significant difference ($p < .05$) between patients' results and a highly significant difference ($p < .001$) between families' results, with the original study by Herz and Melville[4] showing more prodromal symptoms. This difference could have several explanations. One is related to a difference in sampling, since the Atlanta sample included only relatives who were available with the patients prior to relapse and thus were more likely to observe the prodromal symptoms, which resulted in the inclusion of only 80 relatives for the 99 patients. However, the Buffalo sample consisted solely of patients with relapses severe enough to necessitate admission (which was involuntary in more than half of the patients). Again, the sample was small, including only 46 patients. Furthermore, the difference in diagnostic criteria could also be an underlying reason contributing to the difference in results. While our study used DSM-III-R criteria, the earlier study used the DSM-II, which had broader criteria compared with the DSM-III-R. Finally, a cultural element may be involved regarding the family's tolerance and understanding of symptoms along the course of illness in their psychotic relatives.

On the other hand, the fact that relapsing patients in this study gave significantly more accurate responses than their relatives on the administered questionnaire ($p < .05$) suggests that psychiatrists and primary care general practitioners can depend on patients in their assessment for prodromal symptoms. This suggestion may be of paramount clinical importance, since some of the patients may not be living with a reliable family member. However, if the patient drops out of follow-up, this questionnaire can be administered to an available family member. This questionnaire can be used to differentiate patients dropping out owing to loss of insight and starting a process of relapse from those who simply drop out as a result of marked improvement (remission) and feel that they need no more treatment or follow-up. However, it should be emphasized that the best results will be obtained if both the patient and at least one of his or her reliable relatives are interviewed for prodromal symptom assessment. This is expected to improve outcome and decrease relapse rate. This finding was reported in the results of a controlled study[28] of patients who were carefully monitored for prodromal symptoms compared with those receiving usual care. Results showed that prodromal episodes could be detected early, and the relapse rate was reduced by 50%. False positives were rare, and they were outweighed by the dramatic reduction in relapse rates.

The better results (i.e., more accurate and reliable in that more prodromal symptoms were reported) in our group of nonrelapsing parents as compared with those obtained from their relatives may be explained by the former's regaining of insight into their illness, symptoms of this illness, their need for treatment, and their need for self-monitoring and avoidance of relapse. Also, this group of patients may be more independent from their family members, who may thus be unaware of their symptoms.

The highly significant difference between relapsing patients and nonrelapsing patients as well as the significant difference between relapsing patients and healthy

controls on the one hand and the nonsignificant difference between nonrelapsing patients and healthy controls on the other hand indicate that during remission, nonrelapsing patients can be so stable that they become closer to healthy controls than they are to relapsing patients regarding the presence of prodromal symptoms, whether psychotic or nonpsychotic.

Methodological concerns exist on the generalization of our study results. In determining the prodromes of relapse, hallucinations, for example, are obviously psychotic symptoms and no longer "prodromal," so they necessarily predict relapse compared with nonpsychotic symptoms, such as anxiety and depression, both of which are ambiguous and probably reflect different processes at different times and neither of which is necessarily related to relapse nor nosologically specific.[5] In our study, both types of symptoms (psychotic and nonpsychotic) were used for the detection of prodromes of relapse. Again, the individual prodromal symptoms, which were not statistically analyzed in our study, may prove to be important in the longitudinal follow-up of individual patients, e.g., change in eye look, change in appearance, silence, loud voice, hypertalkativeness, absentmindedness, irrational fear, becoming markedly ambivalent, stopping praying, praying without ablution, praying in any direction, staring in a mirror for a long time, sitting alone in darkness, spending a lot of time in the bathroom, and washing hands excessively.

Furthermore, the study carries the disadvantages of all retrospective studies. More than one source of information had to be used in aiming to avoid as much as we could the "hindsight bias" in asking about the prodromal symptoms. There is also a possibility that patients' recall would be unreliable because of the cognitive impairment associated with this illness.[29–31] Thus, an informant from among the reliable family members was also interviewed for more accurate assessment of prodromal symptoms.

Lastly, it is important to emphasize that the data available in this study were derived from clinical groups, which may not fully represent comparable populations over time. The information may, therefore, be biased by the fact that many episodes in highly competent individuals may not be recorded in our statistics and by the fact that those who fill our clinics may be largely poor, premorbid, relapsing patients. This obstacle has been met by earlier researchers who worked with relapsing schizophrenics.[32] Also, the study showed the limitations arising out of the relatively small sample, especially when statistical analyses were done for the individual subtypes of schizophrenia rather than the total sample.

A number of questions remain in implementing such criteria on a routine clinical basis. For example, is relapse indicated only by an increase or reemergence of positive psychotic symptoms, or should negative symptoms also be considered indicative of relapse? Another concern is the duration for which such "prodromal symptoms" have to be present and the frequency of their occurrence to predict that someone is going to have a relapse.

We also recommended the use of short forms of the Early Sign Questionnaire as a component of routine follow-up of schizophrenic patients, as well as teaching the patient and the family to recognize early signs of decompensation (see Table 6). Thus, taking the diagnostic values into consideration, particularly the sensitivity and positive predictive value, suggestion 2 in Table 6 followed by suggestion 1 appear to be the most useful forms. However, suggestion 4 covers a broader spectrum of both psychotic as well as nonpsychotic prodromal symptoms and thus might prove more useful in broader categories of schizophrenic patients.

Future research in the area of prodromes of relapse in schizophrenia should be prospective, longitudinal, and treatment-blind and should use open-ended questions. Another recommendation for future research would be the assessment of, and substantiation of the study with, the objective markers of psychotic episodes, enabling the clinician to detect more precisely the earliest, even subclinical, stages of illness exacerbation or propensity for relapse.

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