

Prodromal Phase of Relapse in Schizophrenia

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The aim of this research was the clinical study of the prodromal period of relapse in schizophrenia, and to show its importance and implications. Subjects for the study comprised 100 outpatients with DSM-III-R schizophrenia (36 patients with paranoid schizophrenia and 64 patients with non-paranoid schizophrenia) and their close family informants. Sociodemographic and clinical characteristics of patients were gathered through a semistructured interview with the patient and his /her family member. A questionnaire for prodromal manifestations was applied by directly interviewing each patient as well as his/her close family informant. The results showed that 53% of schizophrenic patients recognized prodromes of the last relapse, while 69% of their corresponding family members recognized these prodromes ($P < 0.05$). The duration of the prodromal phase in the total sample was about 25 days. The prodromal symptoms showed a high degree of intra-individual consistency, but inter-individual variation. The study concludes that most schizophrenic patients and their family members could become aware of the prodromal period preceding the full relapse, and the duration of this period was sufficient enough to allow for therapeutic intervention to prevent the development of a full-blown schizophrenic relapse. Psychoeducation of patients and their families as regards this phase is highly recommended.

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INTRODUCTION

In medicine, prodromes can be identified with the early symptoms and signs that differ from those of the acute clinical phase. The prodromal phase connotes a time interval between the onset of prodromal symptoms and the onset of characteristic manifestations of the fully developed illness (Fava et al., 1990).

Appraisal of prodromal symptoms has been of importance in clinical medicine for many progressive, dangerous, and treatable diseases in which early detection and timely treatment are crucial (Fava et al., 1990).

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Research on prodromal symptoms in psychiatry has been largely anecdotal and a relatively rare topic of systematic study. An exception concerns schizophrenia, in which appraisal of prodromal symptoms appeared to be important for early therapeutic intervention to prevent the development of full-blown psychotic episodes. Although schizophrenia is a chronic illness with exacerbation and remission there has been surprisingly little systematic study of early signs of relapse. In contrast, there has been a great deal of investigation of early warning signs of dyscontrol of chronic physical illnesses, such as diabetes mellitus; it would be unheard of for physicians not to alert patients and family members to these early danger signals so that the development of serious complications can be prevented.

Psychiatry may not have addressed the questions of relapse in schizophrenia because in the past, most patients were housed in custodial institutions and little attention was paid to fluctuations of the course of the illness. Most patients now live in the community and are visible when they relapse, especially if they become aggressive or disruptive and require rehospitalization (Fava et al., 1990).

In Egypt, clinical experience reveals that the percentage of noncompliance with treatment (maintenance or prophylactic) among schizophrenic patients is high. So, awareness of early signs of relapse and prompt psychiatric intervention may be an appropriate alternative, at least in some patients, to maintenance and prophylactic treatment.

Aim of the Work:

This research aimed to study the clinical aspects of the prodromal stage of relapse in schizophrenic patients characterized by periods of exacerbation and remission.

The *primary objective* was to test the following main and subsidiary hypotheses:

Main hypothesis:

Most patients suffering from relapsing schizophrenic disorders as well as their family members become aware of the occurrence of prodromes preceding the full relapse.

Subsidiary hypotheses:

- Close family members become more aware of the prodromal manifestations than the patients themselves.
- In most patients, the duration of prodromal period is sufficient enough to allow for early psychiatric intervention.
- The prodromal changes are mostly consistent in each patient (i.e. intraindividual consistency) but they show inter-individual variability.

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SUBJECTS AND METHOD

The present work is an analytical, retrospective, hospital-based study which explores the prodromes of relapse in schizophrenia.

1- Sampling:

The study comprised 100 schizophrenic patients and their close family members. Patients were referred cases to Sohag and Assiut Neuropsychiatry Out-patient Clinics, fulfilling the DSM-III-R diagnostic criteria (APA, 1987), who suffered at least 3 relapses of their disorder to allow the awareness of the patient and his family members as regards the prodromes and the course be built up.

Details of all relapses were registered, with a maximum of 10 attacks. However, some patients experienced more than 10 attacks, in such condition, only the first 5 attacks and the last 5 attacks were registered. All patients were in remission.

These patients were classified into either paranoid (no=36) or non-paranoid (no=64) subtypes. This is because the utility of schizophrenic subtypes is most evident in paranoid type, which is commonly characterized by a later and more acute onset, a higher premorbid occupation and social achievement and a more clearly reactive component to the illness than the other subtypes of schizophrenia. The prognosis of paranoid subtype is demonstrably constant and better in both the short and long terms (Lipton and Cancro, 1995). Their age ranged from 20 to 65 years (mean $\pm$ SD of 38.7 ± 9.8 years) 63 were males (63%) and 37 were females (37%).

The *inclusion criteria* were: having at least 3 relapses, in remission, cooperative patient, escorted by at least one cooperative close family member and residence within Assiut or Sohag Gov-

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ernorate. The *exclusion criteria* were: history of organic brain disease, head injury, or drug or alcohol abuse, and mental retardation.

II- Tools of Assessment:

1- The clinical sheet of psychiatric interview, history and mental state examination (Leon et al., 1989).

2- A specially designed sheet (prepared by the first author R.M.) was used to facilitate data collection from each patient at the time of recruitment to the study. This clinical sheet covers items relevant to the present study and are not included in the above mentioned sheet.

3- A specially designed questionnaire 'Prodromes Questionnaire' (in slang Arabic) (prepared by the first author R.M.). It has two forms: one for patients and the second for family informants. The Prodromes Questionnaire is intended to systematically elicit information about different aspects of the prodromal stage.

4- Assessment of socioeconomic status, according to the proposed models of Fahmy and El-Sheribini (1983).

RESULTS

Table (1) shows sociodemographics of the studied patients. Patients of paranoid schizophrenia had a significantly higher mean age (42.6 ± 11.0 years) than non-paranoid schizophrenia patients (36.5 ± 8.3 years) ($p < 0.005$). Also, there is a highly significant difference ($p < 0.001$) between the two subgroups as regards the occupation. The highest percentage of paranoid schizophrenia was observed among unskilled workers (33.3%), while the highest percentage of non-paranoid schizophrenia was observed among housewives (31.3%).

As regards the clinical characteristics, Table (2) shows that paranoid

Table 1
Sociodemographic Characteristics of the Patients

Characteristic	Total Sample (No= 100)	Subgroups		P-Value
		Paranoid (No= 36)	Non-Paranoid (No= 64)	
Age (years) Mean $\pm$ SD	38.7 $\pm$ 9.8	42.6 $\pm$ 11.0	36.5 $\pm$ 8.3	< 0.005
Sex, No. (%)				
Males	63 (63)	22 (61.1)	41 (64.1)	NS
Females	37 (37)	14 (38.9)	23 (35.9)	
Education, No. (%)				
Illiterate	44 (44)	17 (47.2)	27 (42.2)	NS
Educated*	56 (56)	19 (52.8)	37 (57.8)	
Occupation, No. (%)				
No	22 (22)	5 (13.9)	17 (26.6)	P< 0.001
Housewife	30 (30)	10 (27.8)	20 (31.3)	
Others**	48 (48)	21 (58.3)	27 (42.1)	
Marital Status, No. (%)				
Never Married	46 (46)	13 (36.1)	33 (51.6)	NS
Married	35 (35)	13 (36.1)	22 (34.4)	
Others***	19 (19)	10 (27.8)	9 (14.0)	
Socioeconomic, No. (%)				
Very low/ low	85 (85)	30 (83.3)	55 (85.9)	NS
Middle / high	15 (15)	6 (16.7)	9 (14.1)	

* Primary, peraparatory, secondary or university education.

** Student; or unskilled, skilled, semiprofessional or Professional job.

*** Separated, divorced, or widow.

schizophrenia patients have lower mean duration of disorder (12.8 ± 8.0 years) than patients of non-paranoid schizophrenia (13.9 ± 8.0 years). They also have a lower mean number of relapses than non-paranoid patients (6.9 ± 4.6 and 9.1 ± 7.6 , respectively). The two Differences are not statistically significant.

On the other hand, paranoid patients have significantly higher mean age at onset of the disorder (28.1 ± 7.2 years) than patients of non-paranoid type (21.2 ± 4.2 years), ($p < 0.001$).

and their family members in the total sample is significant ($p < 0.05$).

Family members of non-paranoid schizophrenia (73.4%) could recognize the prodromes better than those of paranoid patients (61.1%), $P < 0.05$. The difference between patients with paranoid schizophrenia and their family members was statistically insignificant.

Table (4) shows that, as reported by the patients, the mean durations of the prodromal phase in paranoid and non-paranoid schizophrenia are almost simi-

Table 2
Clinical Characteristics of the Patients

Characteristic	Total Sample (No= 100)	Subgroups		
		Paranoid (No= 36)	Non-Paranoid (No= 64)	P-Value
	Mean $\pm$ SD	Mean $\pm$ SD	Mean $\pm$ SD	
Age at onset	23.6 ± 6.3	28.1 ± 7.2	21.2 ± 4.2	$P < 0.001$
Duration of illness	13.6 ± 7.9	12.8 ± 8.0	13.9 ± 8.0	NS
Number of relapses	8.6 ± 6.9	6.9 ± 4.6	9.1 ± 7.6	NS

Table (3) shows that more than half (53%) of the schizophrenia patients could recognize the prodromes preceding the last relapse, and the difference between paranoid and non-paranoid subtypes is not significant. On the other hand, 69% of the family members could be aware of the prodromal manifestations. The difference between patients

lar (25.1 ± 16.1 and 25.4 ± 15 days). The same pattern was observed when the family members where the source of information. Differences between patients and family members were statistically insignificant. Also, it has to be noticed that the reported durations have wide ranges.

Table (5) shows that there is a high

Table 3
Awareness of Prodromes Preceding the last Relapse among Schizophrenic Patients and their Family Members

Awareness of Prodromes	Total Sample (No= 100)		Subgroups				P-Value
			Paranoid (No= 36)		Non-Paranoid (No= 64)		
	No	%	No	%	No	%	
Patients							
No	47	47	17	47.2	30	46.9	NS
Yes	53	53	19	52.8	34	53.1	
Family Memebbers							
No	31	31	14	38.9	17	26.6	NS
Yes	69	69	22	61.1	47	73.4	
P- Value (Patients vs. Family Members)	< 0.05		NS		<0.05		

intraindividual consistency of the prodromal phases (as regards duration, man-

tween the most frequently reported symptom and the least frequent one. The

Table 4
Duration of Prodromal Phase of Relapse in Schizophrenia

	Total Sample (No= 100)	Subgroups		
		Paranoid (No= 36)	Non-Paranoid (No= 64)	P-Value
Patients				
Range (days)	9-55	10-55	9-50	
Mean $\pm$ SD	25.3 $\pm$ 16.8	25.1 $\pm$ 16.1	25.4 $\pm$ 15.0	NS
Family Members				
Range (days)	10-40	10-40	10-40	
Mean $\pm$ SD	24.5 $\pm$ 11.9	24.4 $\pm$ 11.6	24.6 $\pm$ 12.0	NS
P-value (patients vs family members)	NS	NS	NS	

ifestations and sequence), whether regarded by patients or families. Differences between both study subgroups and between patients vs. families were not statistically significant.

The prodromal features preceding the last relapse as reported by the patients and their family members were about 35 symptoms, with a very wide range be-

most frequent prodrome in the patients' list as well as in the family members' one was insomnia (50% and 59% respectively). Tables (6 and 7) show the first ten, most frequent prodromal symptoms and signs as reported by patients and as reported by their family members. As a whole, the two lists contain 8 common prodromes.

Tables (8 and 9) show that in gener-

Table 5
Intra-Individual Consistency of the Prodromal Phases
of Relapse in Schizophrenia as Reported by the
Patients and their Family Members *

	Total Sample		Subgroups				P-Value
	No	%	Paranoid No	%	Non-Paranoid No	%	
Patients							
consistent	49	92.5	17	89.5	32	94.1	NS
inconsistent	4	7.5	2	10.5	2	5.9	
Total	53	100.0	19	100.0	34	100.0	
Family Members							
consistent	64	92.8	20	90.9	44	93.6	NS
inconsistent	5	7.2	2	9.1	3	6.4	
Total	69	100.0	22		47	100.0	
P-value (patients vs family members)	NS		NS		NS		

* Consistency, as regards duration, prodromal changes and sequence of these changes, across the various prodromal periods in the same patient.

Table 6
Prodromes Preceding the Last Schizophrenic
Relapse as Reported by Patients (no = 100):
The Most Frequent Ten Symptoms

Symptoms	Percent*
Insomnia	50
Depressed Mood	42
Anxiety	45
Decreased Appetite	41
Suspiciousness	39
Somatic Symptoms	39
Abnormal Thought	39
Unusual Behaviour	35
Sense of Presence	25
Dream Changes	23

* Percent of patients who reported the symptom.

Table 7
Prodromes Preceding the Last Schizophrenic Relapse as
Reported by Family Members of Schizophrenic Patients
(no= 100): The Most Frequent Ten Symptoms

Symptoms	Percent*
Insomnia	59
Unusual Behaviour	58
Decreased Appetite	48
Suspiciousness	41
Anxiety	32
Change in Complexion	30
Easily Provoked	29
Depressed Mood	25
Somatic Symptoms	22
Abnormal Thought	20

* Percent of family members who reported the symptom.

Table 8
Awareness of Prodromes of Relapse in Schizophrenia According
to Number of Relapse as Reported by Patients

Order of Relapse	No. of Patients	Paranoid Schizophrenia				Non - Paraniod Schizophrenia			
		No		Yes		No		Yes	
		N	%	N	%	N	%	N	%
First Five Relapses									
1st	100	30	83.3	6	16.7	57	89.1	7	10.9
2 nd	100	23	63.9	13	36.1	50	78.1	14	21.9
3rd	100	18	50.0	18	50.0	39	59.0	25	41.0
4th	86	15	48.4	16	51.6	27	49.1	28	50.9
5th	65	13	59.1	9	40.9	23	53.5	20	48.5
Last Five Relapses									
6th	59	8	42.0	11	57.9	11	27.5	29	72.5
7th	47	6	40.0	9	60.0	8	25.0	24	75.0
8th	40	4	36.4	7	63.6	7	24.1	22	75.9
9th	34	4	40.0	6	60.0	4	16.7	20	83.3
10th	31	4	50.0	4	50.0	4	17.4	19	82.6
P-Value (First vs. Last)				0.001				0.001	
P-Value (Paranoid vs. Non-Paranoid)				NS					

al, with the increase of the number of relapses there is an increase in the awareness of the prodromal phase on the part of the patients as well as their family members. The difference between the first five relapses and the last ones is highly significant ($p=0.001$).

On the other hand, the results of the study showed that awareness of prodromes preceding the last relapse, either by the patients or their family members, had no significant relations to age, sex, education and socioeconomic status of the patients.

Also, our results showed that patients as well as family members most probably sought help at laymen during the prodromal stages of the early relapses, but in the prodromal stages of the last ones, physicians were exclusively sought for help. Differences were statistically significant ($p<0.001$).

The results also showed that a substantial percentage of patients recognized the prodromes without passing

into the full relapse (20% and 23.7% in paranoid schizophrenia and non-paranoid schizophrenia, respectively). Almost all of those who recognized their prodromes without passing into the attack received early treatment.

DISCUSSION

The mean age of schizophrenic patients was 38.7 ± 9.8 years. Patients of paranoid schizophrenia had a significantly higher mean age (42.6 ± 11.0 years) than non-paranoid schizophrenia patients (36.5 ± 8.3 years), $p<0.005$. Kaplan et al. (1994) stated that about 90% of patients in treatment of schizophrenia are between 15 and 50 years of age and paranoid schizophrenia patients are usually older than non-paranoid patients.

As regards gender, 63% were males and 37% were females. Karno and Norquist (1995) stated that there is a striking gender difference in schizophrenia.

Table 9
Awareness of Prodromes of Relapse in Schizophrenia According to
Number of Relapse as Reported by Family Members

Order of Relapse	No . of Patients	Family Members of							
		Paranoid Schizophrenia				Non - Paraniod Schizophrenia			
		No		Yes		No		Yes	
		N	%	N	%	N	%	N	%
First Five Relapses									
1st	100	30	83.3	6	16.7	57	89.1	7	10.9
2 nd	100	23	63.9	13	36.1	50	78.1	14	21.9
3rd	100	18	50.0	18	50.0	44	63.8	20	37.2
4th	86	15	48.4	16	51.6	32	58.2	23	41.8
5th	65	10	45.5	12	54.6	23	53.5	20	64.5
Last Five Relapses									
6th	59	8	42.1	11	57.9	19	47.5	21	72.5
7th	47	6	40.0	9	60.0	14	43.8	18	56.2
8th	40	4	36.4	7	63.6	10	34.4	19	65.6
9th	34	3	30.0	7	70.0	7	29.2	17	70.8
10th	31	2	25.0	6	75.0	5	21.7	18	78.3
P - Value (First vs. Last)				0.001		0.001			
P-Value (Paranoid vs. Non-Paranoid)						NS			

Males have a higher prevalence than females due to the earlier age at onset and also the poor outcome than females. However, Lewis (1992) mentioned that there is equal prevalence of schizophrenia in both sexes.

Illiteracy, unemployment, never married and very low / low socioeconomic levels were high in our sample. In spite of the fact that these features find support in literature (e.g. Lovanger, 1984; Kaplan et al., 1994; Reicher, (198), our sample is not representative because of the inclusion criterion of at least 3 relapses.

Duration of the whole illness was 13.6 ± 7.9 years and the paranoid patients had lower insignificant mean duration of disorder (12.8 ± 8.0 years) than patients of non-paranoid disorder (13.9 ± 8.0 years).

The mean age at onset of schizophrenia was 27.2 ± 8.7 years and paranoid schizophrenia patients had significantly higher mean age at onset than non-paranoid patients (28.1 ± 7.2 and 21.2 ± 4.2 years), $p < 0.001$). Lipton and Cancro (1995) noticed that the mean age of onset in schizophrenia is 27.8 years for males and 31.5 years for females. Kaplan et al. (1994) found that paranoid schizophrenic patients are usually older than catatonic or disorganized schizophrenic patients when they have their first episode of illness.

As regards the ability to recognize prodromes (Table 3), more than half of the schizophrenia patients (paranoid and non-paranoid) could recognize the prodroma preceding the last relapse. Family members of non-paranoid schizophrenia (73.4%) could recognize the prodroma better than those of paranoid patients (61.1%). Differences between the awareness of paranoid schizophrenia patients and their family members were not statistically significant but was statistically

significant in case of non-paranoid schizophrenia patients.

Herz (1985), in his study on 145 schizophrenic patients and 80 relatives, found that 70% of patients and 92% of their relatives were quite aware of prodromal symptoms. Heinrichs et al. (1985), in his study on 38 relapsing schizophrenic patients, found that 24 patients (63%) recognized prodromal symptoms. Nakagomi et al. (1986) reported prodromal symptoms in 79% of relapsing schizophrenic patients. Henmi (1993) studied 61 schizophrenic outpatients in remission, 33 had relapse within the past 20 months were retrospectively examined for prodromal symptoms of relapse. Four weeks prior to the relapse, 63.6% manifested prodromal symptoms. Rakhawy (1994) stated that 52.5% of his schizophrenic patients and 44% of their family members were aware of prodromal changes.

The percentages of the most common symptoms is relatively small. The majority of the symptoms are present in less than 50% of patients. Also, there is a very wide range between the most frequently reported symptom and the least frequent one. This may indicate higher inter-individual variability of the prodromal phases of relapse. Also, the wide range of the duration of the prodromal phase as reported in this study may indicate the same, inter-individual variability. Insomnia, depressed mood, anxiety, decreased appetite and suspiciousness were among the most frequently reported prodromes.

Hopkinson (1965) stated that about 30% of relapsing schizophrenic patients showed a prodromal phase characterized by tension and vague feelings of anxiety and more seldom symptoms such as indecision and impaired concentration.

Donlon et al. (1973) reported anxiety, insomnia, difficulty in concentration,

lowered drive and feeling of excitement as prodromal symptoms for schizophrenic relapse.

Herz (1985) and Kumar et al. (1989) found the most frequently cited possible prodromal symptoms in schizophrenic patients to be consisting of mood changes such as tension, irritability, depression, anxiety, withdrawal and vegetative changes such as disturbed sleep and loss of appetite.

The mean duration of prodromes in schizophrenic patients was 25.3 ± 16.8 days, with nearly the same results in both paranoid and non-paranoid patients (Table 4). The same observed with family members. Birchwoord et al. (1989) reported up to 50% subjects studied have been found to progress through a prodromal period to psychotic breakdown within 4 weeks.

This period can be sufficient enough for the patients and their families to seek medical help. This will allow for early intervention and, probably, abortion of the full relapse.

Herz (1985) suggested that the modal prodromal period is 2 weeks and there is consistency within individuals from relapse to another in the nature and timing of early signs. In the present study, almost all relapses were consistent, whether regarded by patients or families, in the same individual patient (Table 5). This finding could facilitate psychoeducation of individual patients and their families about the prodromal phase. However, considerable inter-individual variability is found in this respect. This point should also be considered in psychoeducation.

The study also showed that with progress of the disorder, percentages of relapses with recognized prodromes by patients and their family members significantly increased in all groups (Table 8).

Nevertheless, the psychiatrist must inform the patients and their families about the prodromal changes and the importance of therapeutic interventions at that time since the first episode, and not to wait that they have to know by themselves.

Patients, as well as their family members, most probably sought help at laymen during the prodromal stages of the first attacks, but in the prodromal stages of the last ones, psychiatrists were exclusively sought. Differences were statistically significant. In Upper Egypt ignorance about psychiatric treatment is highly prevalent and superstitions are well believed in. However, with increasing severity and frequency of the relapses and the quacks failing to induce improvement in the patient's condition, the correct alternative (the physician) is usually sought, who usually proves success with such patients.

A substantial percentage of patients recognize the prodromes without passing into the full attack. Almost all of those who recognized their prodromes without passing into full relapse received early treatment. So, the early/abortive treatment is crucial in preventing the relapse.

Overall, and within the context of the limitations of the study, the findings may be taken as evidence supporting the study main and subsidiary hypotheses. And, based on these findings, psychoeducation of schizophrenic patients and their family members as regards the prodromal changes of relapse is highly recommended. Intraindividual consistency of these prodromes could facilitate this. The duration of the prodromal phase is sufficient to seek help and to have the appropriate management, aiming at abortion of the impending relapse.

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L'épisode avant la relapse de schizophrénie

Cette étude a été conduite dans la but de distinguer l'aspect clinique de la période précédé immédiatement la relapse de schizophrénie et son importance.

Nous avons fait passer à un échantillon de 100 patients ayant le diagnostic de schizophrénie selon les critères du DSM-III-r. et leurs parents.

Un entretien semistructuré avec les patients et leur parents ainsi qu'une évaluation psychométrique de manifestation de cette période.

Les résultats ont montré que 53% des patients reconnaissent bien cette période.

69% et des membres de la famille des patients reconnaissent la durée de cette épisode (à peu près 25 jour) suffisante et permet l'intervention thérapeutique pour réduire les symptômes du relapse.

مرحلة بوادر الانتكاس في مرضى الفصام

يهدف هذا البحث إلى دراسة الجوانب الإكلينيكية المختلفة لبوادر الانتكاس في مرضى الفصام. وقد أجريت هذه الدراسة على مائة شخص مريض بالفصام (٣٦ يعانون من فصام بارانوي و٦٤ مريضاً يعانون من فصام غير بارانوي) وذلك بالإضافة إلى أفراد عائلاتهم القريبين منهم. وقد تم جمع البيانات الخاصة بالنواحي الاجتماعية، والديموجرافية، والكلينيكية من المرضى وذويهم، كما تم تطبيق استبيان مفصل عن بوادر الانتكاس على المرضى، وكذلك من خلال المقابلة المباشرة مع أهاليهم.

وقد أظهرت نتائج الدراسة أن ٥٣٪ من مرضى الفصام بنوعية كانوا على وعي ببوادر الانتكاس الأخيرة، بينما تعرف ٦٩٪ من أهل المرضى على هذه البوادر، وكانت المدة التي استغرقتها بوادر الانتكاس حوالي ٢٥ يوماً، وكانت بوادر الانتكاس في مرض الفصام متسقة بالنسبة للمريض الواحد ومختلفة بين المرضى.

ونستخلص من ذلك أن معظم المرضى وأهلهم يمكنهم التعرف على بوادر الانتكاس، وأن مدتها تسمح بالتدخل العلاجي السريع لمنع الانتكاس الكاملة، وتوصي الدراسة بضرورة توعية المرضى وعائلاتهم من حيث بوادر الانتكاس مع ضرورة التدخل المبكر في هذه المرحلة لمنع الانتكاس الكاملة.