Retrospective study of prodromal symptoms in schizophrenia

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Estudio retrospectivo de los síntomas prodrómicos en la esquizofrenia

Summary

Introduction. *There are some non-psychotic symptoms that can forecast the onset of psychosis. Discovering the differences between the symptoms that lead to disease and those that do not makes it possible to identify them and permits early treatment of the disease.*

Methods. *A sample of 689 schizophrenic patients was analyzed retrospectively. This sample was obtained from the clinical records database of the University Psychiatric Hospital Institut Pere Mata. Data were analyzed with the SPSS version 9.0 statistical package.*

Results. *The most frequent prodromal symptoms of the sample were the delusional ones, the disorganized ones and the neurotic ones. The prodromal symptoms were equally distributed in both genders. In the subtypes, paranoids showed more delusional symptoms, whereas the non-paranoids presented more disorganized symptoms. Acute onsets had more delusional prodromal symptoms whereas the insidious onsets showed more disorganized ones.*

Conclusions. *In the prodromal stages of shizophrenia, we can also find the community neurotic prevalences regarding gender. The higher rate of neurotic symptoms in the non-paranoid subtype would be explained by the inclusion of the schizoaffective category, whereas the higher rate of disorganized symptoms categories would be due to the hebephrenic and simple categories. The latter would also explain the prodromal differences in the onset type.*

Key words: *Schizophrenia. Prodromal symptoms. Sex. Subtype. Onset type.*

Resumen

Introducción. *Existen unos síntomas prodrómicos que pueden anunciar el inicio de las psicosis, entre ellas, la esquizofrenia. Descubrir la diferencia entre los síntomas que conducen a la enfermedad de los que no permitiría identificarlos y empezar a tratar la enfermedad de forma precoz.*

Metodología. *Análisis retrospectivo de una muestra extraída de la base de datos informatizada de las historias clínicas del Hospital Psiquiátrico Universitario Institut Pere Mata. Esta muestra consta de 689 pacientes esquizofrénicos. Los datos se analizan con el paquete estadístico SPSS versión 9.0.*

Resultados. *En esta muestra los síntomas prodrómicos más frecuentes son los delirantes, los desorganizados y los neuróticos. Respecto al sexo, los síntomas prodrómicos se distribuyen de forma uniforme. En cuanto al suptipo, los paranoides muestran más síntomas delirantes y los no paranoides presentan más síntomas desorganizados. Los inicios agudos tienen síntomas prodrómicos más delirantes y los insidiosos más desorganizados.*

Conclusiones. *En las fases prodrómicas de la esquizofrenia también se reflejan las prevalencias neuróticas comunitarias en cuanto al género. La mayor frecuencia de síntomas neuróticos en el subtipo no paranoide se explicaría por la inclusión de la categoría esquizoafectiva, mientras que la mayor frecuencia de síntomas desorganizados se debería a las categorías hebefrénica y simple. Esto último también explicaría las diferencias prodrómicas del tipo de inicio.*

Palabras clave: *esquizofrenia, síntomas prodrómicos, sexo, subtipo, tipo de inicio.*

INTRODUCTION

Conceptual framework

The review of the third version of the *Diagnostic and statistical manual of mental disorders* (DSM-III-R)[1] defines the prodromal phase of schizophrenia as a deterioration of activity before the active phase that is not due to any alteration of the mood state or to any psychoactive substance use caused disorder. Later, the fourth version (DSM-IV)[2], in the section on the course of schi-

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zophrenia, comments that the prodromal phase is manifested by a slow and gradual development of different signs and symptoms.

In the guidelines for diagnosis, the tenth version of the *International Disease Classification* (IDC 10)[3] explains that if we study it retrospectively, a prodromal phase can appear in which certain symptoms and behavior in general precede the onset of the psychotic symptoms in months or even weeks. It adds that, given the difficulty to define the onset of the disease in time, the duration guideline of one month only refers to the specific symptoms named and not to any of those that appear in the non-psychotic prodromal phase.

In 1992 Loebel et al[4] defined prodrome as the time interval between the onset of the unusual behavior symptoms and the appearance of psychotic symptoms. Essentially, the period of prepsychotic alteration that occurs before the onset of disease is understood to be prodrome. In 1996, Yung and McGorry[5] defined prodrome as the alteration period that precedes a first psychotic episode.

In 1999 Parnas[6] explained that «the prodromal symptoms occur in a substantial proportion of pre-schizophrenics, followed by a pre-short psychotic period with the crystallization of a psychotic syndrome» and defined the prodromal period as the phase immediately before psychosis, in which the first indicators of the disease are manifested. Even more, he clarifies that the notion of prodrome means a clear change from that which is normal to a change that announces a new process that affects the individual.

From the neurobiological point of view, the prodromal phase seems to be a new and differentiated process and represents a certain change, perhaps accumulative, in the neuronal substrate (a *morbid process,* in the Jasperian sense) with the characteristic peaks of intensity available in the formation of a psychotic syndrome. The prodrome should mean a period of neurodynamic instability or *transition phase,* when a system moves from one form of organizational stability to another. In this same line, in 1999, Miller and McGlashan[7] commented that the neurobiological deficit associated with the onset of the disease should be more active and harmful in the early stages, thus it is important to detect the prodromal states of these disorders early.

Previous findings

The findings obtained by previous studies on the prodromal symptoms are very uniform. The up-dated review of Peralta and Cuesta[8] comments on the studies of Kraepelin et al (1927)[9], in which the prodromal symptoms that are presented are: thought fragmentation, decrease in volition and emotional response; greater vivacity, dejection and depression, tendency to distraction, lack of interest, surprising activity and decreased hunger and sleep. In 1936, Bumke[10] described complaints of weakness, dejection, fatigue and decreased concentration, and somatic symptoms such as palpitations, vertigo, loss of hunger, sensation of change and not being able to think clearly and bouts of impressions.

In 1966, Chapman[11] spoke about some early specific changes with neurotic symptoms, anxiety and depression, as reaction to changes. These changes are characterized by an attention disorder, blocked thought, modification of perception and motility disorder. Koehler and Sauer (1984)[12] commented that the basic symptoms are subjective complaints of deterioration in cognition, emotion, motricity, autonomic functioning, body sensation, energy, external perception and tolerance to stress.

In 1992, Klosterkötter[13] described non-specific subjective complaints on the course of thought, blocks, interferences, complaints of lack of control, discrimination disorders between thoughts and auditory images, autopsychic depersonalization and discrimination disorders between auditory images and acoustic perceptions. In 1995, Jackson[14] demonstrated the following prevalence of prodromal symptoms in schizophrenia: 75.5% of social isolation, 62.8% of deterioration in functioning, 53.3% of rare or special ideation, 33.7% of lack of initiative, interest or energy, 33.3% of blunted or inappropriate affectivity, 29% of vague, metaphoric or digressive speech, 25.5%, of distinctive behavior, 23.7 % of unusual perceptive experiences and 23.3 % of deterioration of personal hygiene.

Strakowski (1995)[15] commented that 17% of psychotics present anxiety disorders, 17% alcohol abuse, 11% drug abuse, 11% post-traumatic stress disorders and another remaining 11% obsessive-compulsive disorders. In 1996, Yung and McGorry[15] observed that the nine most frequent prodromal symptoms are: decreased concentration and attention, apathy, sadness, sleep disorders, anxiety, social withdrawal, suspiciousness, functioning deterioration and irritability. Häfner[16], in turn, found anxiety in 18%, restlessness in 17%, depression in 16%, sleep and eating disorders in 13%, thought and concentration disorders in 13%, withdrawal and suspiciousness in 10%, loss of energy in 9%, reference deliriums in 7% and work difficulties in the remaining 7%.

OBJECTIVES

General objectives

The importance of detecting the onset of a disease early is found in early prevention, identification of biological markers and in psychotic psychopathogeny[17]. In 1938, Cameron[18] stated that «the early detection of many disorders prevents serious later health problems». More recently, in 1992, Falloon[19] and in 1993, Birchwood[20] pointed out the need for early diagnosis to control the psychological, biological and social disorder that results from schizophrenia.

The presence and duration of the prodrome can be indicative of the course and prognosis of psychosis and the different subtypes. Some authors[21,22] have proposed a similarity between this initial phase and the phase prior to relapse. This relationship would make it possible to prevent relapse.

Another motive of interest in the identification of the prodromes is found in the development of neurobiological and phenomenological theories of psychosis. Knowing how the disease emerges could contribute information on the pathogenesis of the psychosis and would contribute to determining prediction markers[5].

Specific objectives

This study proposes to evaluate the prodromes that appear in a sample of hospitalized schizophrenic patients in the Hospital Universitario Psiquiátrico Institut Pere Mata de Reus based on some variables having clinical interest such as gender, subtype of schizophrenia and type of onset, in order to be able to obtain information to clarify some of the already mentioned points and to be able to establish comparisons with other authors who have studied the subject of prodromal symptoms in schizophrenia.

METHODOLOGY

The usual form of evaluating prodromal symptoms is by a retrospective study of the onset of the disease.

The sample information has been obtained from the computerized database of the clinical histories of the patients over 18 years who have a clinical diagnosis of schizophrenia according to the ICD-9 (code 295) who have been admitted to the University Psychiatric Hospital Institut Pere Mata, both in the acute and subacute unit as well as in the middle and long stay one.

The clinical histories are based on the system of the Association for the Methodology and Documentation in Psychiatry (AMDP)[23]. The history contains some sections that refer to the first symptoms: the year of onset of the first symptoms, first symptom that appeared and type of onset. The source of information of the first symptoms appeared is provided by a family member or direct caretaker of the patient at the time of admission to avoid bias of the information distorted by the mental state of the patient. The first symptom appears in the clinical history in a non-coded way and later, it is coded according to the AMDP European system[23]. This is formed by a group of 166 symptoms organized into twenty groups, which are: speech and language disorders, formal thought disorders, intelligence, awareness disorders, orientation disorders, attention and memory disorders, perception disorders, delusional ideas, disorders of the experience of the self, mood state disorders, tremors and phobias, somatomorphic symptoms, dissociative symptoms, impulses and psychomotricity, eating behavior disorders, sleep disorders, sexual disorders, simulation and factitious disorders, disorders due to consumption of toxic substances and other disorders in which the following are included: decreased sociability, increased sociability, suicidal ideation, aggressivity, disocial behavior, delinquency, persistent transformation of the personality, disorders of habits and of control of impulses and others, among which behavior alteration is considered.

The variables of interest in relationship with prodromal signs and symptoms are: gender, subtype of schizophrenia and type of onset of the disease.

The variable gender, in schizophrenia, is always of interest since clear clinical differences are observed between men and women, for example in age of disease onset[2,3]. The sample was divided into two subtypes: paranoid and non-paranoid, division that already appeared in other studies, as for example in that of Phillips[24] and Huang[25]. The type of disease onset has been divided into acute and insidious.

After, the information is introduced in the database of the version 9.0 of the Statistical Package of Science Social (SPSS) (SPSS, Inc., Chicago, Illinois) for Windows (Microsoft, Seattle, Washington), where the posterior data processing has been done.

RESULTS

The sample is formed by 689 patients diagnosed of schizophrenia.

Regarding gender, there were 257 women (37.3%) and 432 men (62.7%).

The subtypes showed the following distribution: paranoid (48.2%) compared to non-paranoid (51.8%) while the type of onset found was mostly insidious (60.4%), in comparison to 39.6% who experienced an acute onset for the 672 patients for whom this information is known.

The most frequently occurring prodromal symptoms (greater than 4%) were grouped into: *delusional symptoms,* in which persecutory and harm ideation, reference ideas and delusional ideation; *disorganized symptoms* formed by behavior disorder, decreased sociability, rare behaviors and aggressivity and in *neurotic symptoms* with depression, insomnia and anxiety. The remaining prodromal symptoms occur in a percentage under 4%.

Regarding gender, the most frequent prodromal symptoms coincide and the percentage of frequency is uniform regarding the delusional and disorganized symptoms. Women show slightly greater percentages in the neurotic prodromal symptoms (15.6) compared to men (11.9%).

Differences are observed between the most prevalent prodromal symptom of the paranoid and non-paranoid subtypes. While the disorganized symptoms present as the most frequent (25.8%) in the non-paranoids, the paranoids show delusional symptoms (26.8%) of the cases.

The insidious forms manifest differentiated prodromes of the acute onsets. In the acute forms, delusional prodromal symptoms are observed as most frequent (21.8%), while the disorganized symptoms appear in 27.5% of the cases in the insidious onsets.

All these results are summarized in table 1.

CONCLUSIONS

The prodromal symptoms that appeared with the greatest frequency in our sample of schizophrenic patients are

TABLE 1. Percentages of prodromal symptoms in each variable studied

	Gender n = 689		*Subtype n = 689*		*Onset type n = 672*	
No. of the variable (%)	*Women 257 (37.3)*	*Men 432 (62.7)*	*Paranoids 332 (48.2)*	*Non-paranoids 357 (51.8)*	*Insidious 406(60.4)*	*Acute 266 (39.6)*
Prodromal symptoms (with percentages > 4%)						
Delusional symptoms						
Delusional ideas of persecution and harm	10.5	9.7	13.0	7.3	7.6	13.2
Delusional ideas of reference	5.1	6.0	6.6	4.8	6.9	4.1
Delusional ideas	3.5	4.6	7.2	1.4	4.2	4.5
Total delusion symptoms	19.1	20.3	26.8	13.5	18.7	21.8
Disorganized symptoms						
Behaviour disorder	7.0	8.3	5.1	10.4	7.6	7.1
Decreased sociability	6.6	8.3	5.7	9.5	10.8	3.0
Rare behaviors	6.6	5.6	6.0	5.9	5.4	6.8
Aggressivity	4.7	3.5			3.7	4.5
Total disorganized symptoms	24.9	25.7	16.8	25.8	27.5	21.4
Neurotic symptoms						
Depression and sadness	6.2	4.9	4.2	6.4	5.7	5.3
Insomnia	5.1	2.1				
Anxiety and internal restlessness	4.3	4.9	4.5	4.8	4.2	5.3
Total neurotic symptoms	15.6	11.9	8.7	11.2	9.9	10.6
Total of prodromal symptoms with percentage > 4%	59.6	57.9	52.3	50.5	56.1	53.8
Total of prodromal symptoms with percentage < 4%	40.4	42.1	47.7	49.5	43.9	46.2
Total	100.0	100.0	100.0	100.0	100.0	100.0

similar to those found by other authors: delusional ideas, whether of persecution or harm, and ideas of reference or allusion reported by Häfner[16]; behavior disorder and rare behaviors described by Jackson[14], social isolation observed by Jackson[14], Yung and McGorry[5] and Häfner[16], and depression and anxiety described by Kraepelin[9], Strakowski[15], Yung and McGorry[5] and Häfner[16].

The prodromal symptoms that do not appear in our study and that are also mentioned in the literature are: tendency to distraction or decreased concentration and apathy or lack of energy, by Yung and McGorry[5] and deterioration in functioning by Koehler and Sauer[12], Jackson[14], Yung and McGorry[5] and Häfner[16]. These differences could be due to sample or methodological differences, such as the deterioration of functioning, which does not appear because it is not assessed as a symptom in the psychopathology examination used.

In regards to the differences between men and women, two circumstances stand out: on the one hand disorganized symptoms that make up the constellation that could be included either within syndromic inspecificity of schizoid (above all in the sense of negative-behavior symptoms) or even with the characteristics of premorbid personality disorder; in both cases, the literature[26] shows that the frequency is greater in men than in women. In this study, both frequencies are similar (24.9% in women and 25.7% in men). We do not believe that this is due to any specific cultural pattern of our geographic area, however, we consider that it is an interesting subject to go into in more depth in future studies.

On the other hand, the *neurotic prodromal symptoms* of women are a little more frequent than those of men. This is also observed in the community epidemiological studies on psychiatric disorders in which the women present greater percentages of neurotic disorders (anxiety disorders in 12.3% of women compared to 4.5% in men)[27], so that it may simply be a reflection of the community psychopathology itself in schizophrenia.

Delusional symptoms are the same in both genders and our observation is that they would correspond to most of the paranoid schizophrenias that start directly with positive symptoms and in which there are generally no differences in gender.

This difference between paranoid and non-paranoid schizophrenia is clearly reflected in greater frequency of *delusional symptoms* which, as is to be expected, appear by double the percentage of the paranoid subtype versus that of non-paranoid. Among the non-paranoid forms, hebephrenic and simple subtypes have been included; their characteristics are exactly those of a behavior disorder and this would explain the differences regarding the second group of symptoms *(disorganized symptoms)* that are more frequent in the non-paranoid group.

Although we think that the *neurotic symptoms* would have a uniform distribution between both subtypes, in this study there is a slightly superior tendency in the non-para-

noid subtype and this may be due to the inclusion of the schizoaffective type which generally appears as a differentiated category in other studies. In this study, a wider concept of schizophrenia was used and that is why it has been included.

The acute onsets initiate with *more delusional prodromal symptoms* and the insidious ones present *more disorganized symptoms.* This agrees with the natural course itself of the schizophrenic pictures represented by the mentioned prodromal symptoms, that is, the paranoid pictures appear in a more acute form than the disorganized and/or schizoaffective subtypes.

The limitations of this study are subject to those of the design itself of a retrospective study that can be summarized in:

1. Difficulty to determine the time period and what occurs in it.
2. Memory can be influenced and affected by many factors.
3. The limit between prepsychotic changes and those that are frankly psychotic is not clearly defined.

Future directions

1. It is necessary to operatively define the prodromal symptoms that are precursors of schizophrenia to establish the risk factors, and according to the their importance, determine the onset of treatment.
2. Relate the prodromal symptoms with clinical and biological variables.
3. Study the prodromal symptoms in all the types of psychotic disorders and without being confined to schizophrenia.
4. Investigate sensitivity, specificity, positive and negative predictive value.

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