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Duration of untreated psychosis as predictive and prognostic factor in the course of first episode psychosis

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Introduction. Recently, many studies have focused on the duration of untreated psychosis (DUP) in order to clarify if DUP could be one of the factors that would influence prognosis of psychotic disease.

Material and methods. We present a one year follow - up study with 90 medication native, first episode psychotic patients. The likely prognosis factors that could influence in the outcome of the disease were measured. Therefore, we used a protocol including the following scales: PANSS, Psychosocial Stress Global Assessment scale (DSM IIIR), Global Assessment of Functioning scale (GAF-EEAG), Clinical Global Impression (CGI), Montgomery-Asberg scale for the depression, Young mania rating scale, abnormal involuntary movements scale, UKU scale for extrapyramidal symptoms and Premorbid Adjustment scale (Cannon-Spoor). Assessments were made every three months for 1 year. A statistical analysis of data was performed.

Results. As a result, it was concluded that there was no relationship between a long duration untreated psychosis and a worse outcome of the illness in our sample. The only related factors with the prognosis were premorbid adjustment and the type of disease onset. Hence, the patients with a better premorbid adjustment and an acute onset of psychosis had a better outcome.

Conclusion. Our study represents more evidence in favor of the independence of DUP and disease outcome.

Key words:
Duration of untreated psychosis. First episode psychosis. Outcome. Premorbid adjustment. Onset.

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El tiempo de psicosis no tratada como factor predictivo y pronóstico en el curso de los primeros episodios psicóticos

Introducción. El tiempo de psicosis no tratada ha estado en el punto de mira de numerosis artículos que intentan clarificar si podría resultar ser uno de los factores que condicionaría el pronóstico final de la enfermedad psicótica.

Material y métodos. Presentamos un estudio realizado en 90 pacientes con un primer episodio psicótico que no habían tomado medicación previamente en el que se evaluaron los posibles factores pronósticos que influirían en la evolución de la enfermedad. A tal efecto se utilizó un protocolo que incluía las siguientes escalas: PANSS, escala de Valoración global de estrés psicosocial (DSM IIIR), evaluación de actividad global (GAF-EEAG), impresión clínica global (ICG), escala de Montgomery-Asberg para la depresión, escala de manía de Young, escala de movimientos anormales, escala UKU para síntomas extrapiramidales y la escala de ajuste premórbido (Cannon-Spoor). El seguimiento se realizó durante 1 año con evaluaciones cada 3 meses.

Resultados. Tras el análisis estadístico de los datos se concluyó que un tiempo de psicosis prolongado no se asociaba en nuestra muestra a una peor evolución de la enfermedad. Los únicos factores relacionados con dicho pronóstico resultaron ser el ajuste premórbido y el tipo de comienzo de la enfermedad. Así, pacientes con un mejor ajuste premórbido y un inicio de enfermedad agudo presentaban una mejor evolución.

Conclusiones. Nuestro trabajo muestra una evidencia más en favor de la independencia del pronóstico final y el tiempo de psicosis sin tratar.

Palabras clave:
Tiempo de psicosis sin tratar. Primer episodio. Pronóstico. Ajuste premórbido. Inicio de la enfermedad.

INTRODUCTION

The early phases of psychotic disease have aroused special interest in recent years. This is partially due to the possibility of modifying the disease course if there is early intervention. However, in spite of the therapeutic advances in recent years, the prognosis of psychotic disease continues to be gloomy in some cases. The constant search for factors that may participate in this prognosis and also be modifia-

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ble has caused investigators to focus their attention on the duration of untreated psychosis (DUP) in recent decades. This has added a new gateway for early treatment of these patients to the already known difficultly changeable factors, such as age of disease onset, gender and genetic vulnerability to the prognostic factors. In this way, confirmation of DUP as a prognostic factor of the disease would place early intervention programs aimed at reducing duration of untreated disease as the key to the approach of diseases such as schizophrenia.

According to several studies published, treatment onset is generally delayed for a mean of 1-2 years from when the first psychotic symptoms appear[1-3]. This indicates that there is considerable time variation between the studies in regards to treatment onset delay.

Many studies have associated prolonged DUP with a worse prognosis and insufficient treatment response[4-6]. This association has served as a base to initiate an early intervention program[7].

DUP has also been related with substantial functional deterioration, increase in resistance to treatment and increased relapse rate[8]. Although this relationship has been independent of other prognostic factors in some studies[9], the last correlation of this influence must still be solved. There are already investigators who state the possible participation of other prognostic factors that would also act as confounding factors in this relationship. Among them, they mention premorbid adjustment, disease type, type of onset of this disease or sociodemographic profile of the patient[10].

As reflected in some of the studies conducted, a statistically significant relationship is observed between DUP and prognosis at 12 months of disease onset, the influence of the clinical intervention on prognosis being limited in these cases. However, patients with a shorter DUP seem to benefit from the clinical intervention models, this leading to better functional prognosis at 12 months[11]. This fact would orient towards the need of creating different therapeutic strategies for each group of patients. The impact of early detection programs seems more complex than originally thought. On the one hand, if the DUP is a modifiable prognostic factor, there is the possibility of suggesting that it could also be a predictive factor of such prognosis. In this way, it would be possible to determine which patients would have a worse evolution of it from the onset of the disease.

This present study aims to determine the prognostic factors that would have a predictive capacity on the course of the psychotic disease and response to treatment in a group of first psychotic episode patients. To do so, special attention has been given to the following variables: premorbid adjustment, duration of untreated psychosis, type of disease onset, sociodemographic profile and existence of family background of psychosis.

MATERIAL AND METHODS

This is a prospective, open, observational, longitudinal and repeated measures clinical study in which those persons affected by a first psychotic episodes in the health care areas corresponding to the Hospital de Cruces and Hospital de Zamudio (Vizcaya) during the 2000-2002 period were included. Most were seen on their first hospital admission. In every case, they fulfilled diagnostic criteria for a first psychotic episode (FIS 01/1455 Project).

METHODS

Sample

Finally, 90 patients were included. Of these, 68 were re-evaluated at six months (72.6%) and 63 were evaluated in the one year follow-up (70%).

Evaluations were conducted at baseline, 6 and 12 months. Sociodemographic data and the diagnosis according to DSM IV criteria (SCID I) were collected in the baseline evaluations. Diagnosis according to DSM IV criteria was confirmed by the investigator and another psychiatrist trained for this. Background or organic diseases and possible previous psychiatric disorders of the patients were taken into account in the clinical history. Blood and urine analyses, EKG and brain CT scan were also done to rule out any organic disease.

Duration of the untreated psychosis (DUP) was established for each patient, reviewing the relevant information in his/her clinical history and by an interview of the patient and his/her relatives or closest family or caretakers. Date of the first positive and negative psychotic symptom was taken into account. The first behavioral alteration reported by the patient or his/her family was also recorded.

Measurement instruments

Instruments and clinical indicators on the disease course and response to treatment were used. These were: Psychosocial Stress Global Assessment scale (DSM IIIR), Global Assessment of Functioning scale (GAF-EEAG), Clinical Global Impression (CGI), PANSS scale, Montgomery-Asberg scale for depression, Young mania rating scale, Abnormal Involuntary movements scale, UKU scale for extrapyramidal symptoms, premorbid adjustment scale (Cannon-Spoor). Family psychiatric background and toxic consumption were also taken into account. All the patients signed an informed consent.

Statistical analysis

Repeated measures analysis of variance and covariance was used to estimate the effect of potential prognostic fac-

tors on the disease course and response to treatment. Four measurements of the indications of the disease course and response to treatment were used: on admission, discharge, follow-up at 6 and 12 months. In order to simultaneously check the effect of the type of disease onset (acute/chronic) and premorbid adjustment, the type of onset was included as factor and premorbid adjustment as covariable of the symptoms and severity of psychotic disorder.

In order to estimate the association between different subscales of premorbid adjustment and duration of untreated psychotic symptoms, Pearson's bivariate correlation coefficient with bilateral contrast was used. The Student's *t* test was also used to compare mean scores between patients with DUP less than or greater than one year on the PANSS subscales in the baseline evaluation and 6 and 12 month follow-ups and the premorbid adjustment evaluated with the Cannon-Spoor and Phillips scales.

RESULTS

A total of 58 of the 90 patients enrolled were men (64.4 %) and 32 women (35.6 %). Average age was 26.7 years (SD = 10.4), with a range of values between 17 and 72 years. In regards to civil status, 84.4 % of the patients were single and lived with their family of origin (76.7 %). A total of 40 % had completed elementary school or equivalent, while 21 % only had primary studies or had not completed them and only 34 % had completed vocational training or high school. Most of the patients were not working (61.1 %).

Table 1 summarizes the diagnoses regarding psychotic disorder and mood state (SCID-I). At one year, the most frequent diagnosis was schizophrenia (27.8 %), followed by schizophreniform disorder (14.4 %). Affective disorders accounted for 8.8 % of all the sample.

Table 1 Diagnostic stability at one year

Diagnosis	Baseline (n = 90)	6 months (n = 68)	12 months (n = 63)
Substance induced psychotic D.	3.3 %	1.1 %	–
Schizophrenia	22.2 %	25.5 %	27.8 %
Schizophreniform D.	21.1 %	18.9 %	14.4 %
Delusional D.	7.8 %	4.4 %	3.3 %
Brief psychotic D.	23.3 %	4.4 %	9 %
Schizoaffective D.	1.1 %	2.2 %	2.2 %
Unspecified psychotic D.	15.6 %	5.6 %	3.3 %
Bipolar D.	5.5 %	6.6 %	6.6 %

In the following table, we can observe the most frequent diagnoses of the sample at one year of study.

Table 2 Relationship at one year of the different scales with different prognostic factors

	PANSS	CGI	EEAG	Depression	Mania
Gender	ns	ns	ns	ns	ns
Onset	*	*	ns	*	ns
Symptoms without treatment	ns	ns	ns	ns	ns
Family background	ns	ns	ns	ns	ns
Childhood adjustment	*	*	**	ns	*
Early adolescence adj.	ns	ns	*	ns	ns
Late adolescence adj.	ns	ns	ns	ns	ns
Adult age adjustment	ns	ns	ns	ns	ns
General adjustment	ns	ns	ns	ns	ns
Change in scale	***	***	***	***	***

ns: the factor has no statistically significant effect in the course and evolution of this indicator of disease and response to treatment. * $p < 0.1$ in the F test for repeated measures analysis. ** $p < 0.01$ in the F test for repeated measures analysis *** $p < 0.001$ in the F test for repeated measures analysis.

Predictive and prognostic factors of the course and response to treatment

Table 2 shows the relationship between potential predictive and prognostic factors and disease course and response to treatment. Table 3 shows the results after jointly analyzing the possible effect of both predictive and prognostic factors on the psychotic disease course and response to treatment. We observed that:

– The total score on the PANSS scale decreases substantially and with statistical significance during the study. The patients improve clinically during the follow-up year. In the same way, it is seen that this score decreases in the patients with acute onset of the disease (less than 6 months) more significantly than in patients who began the psychosis with a more chronic

Table 3 Relationship between prognostic factors and disease course

	PANSS (total)	CGI (severity)
Onset (acute/chronic)	*	*
Premorbid adjustment (childhood)	ns	*

ns: the factor has no statistically significant effect on the course and evolution of this indicator of disease and response to treatment. * $p < 0.1$ in the F test for the repeated measures analysis.

onset. Equally, it was observed that better premorbid adjustment in childhood is significantly associated to better evolution in this score (fig. 1).

- The severity of the disorder decreases substantially and significantly during the year of treatment, considering the evolution of the CGI scale. Again, an acute onset of the disease and better premorbid adjustment during childhood were significantly associated to better course of the disorder (figs. 2 and 3).

- Global activity (EEAG), depression (Montgomery-Asberg) and mania (Young scale) evolved positively and significantly during the study year. Acute onset of the disease was related with better course of depressive symptoms. In the same way, it was reflected that better premorbid adjustment during childhood is associated to better evolution of global activity and manic symptoms.

Duration of untreated symptoms (DUP) and course of positive and negative symptoms (PANSS)

If we apply a repeated measures analysis of variance to contrast if the DUP is associated with the course of the positive and negative symptoms, we will observe that no association is found with the course or average score of the symptoms during the year of the study.

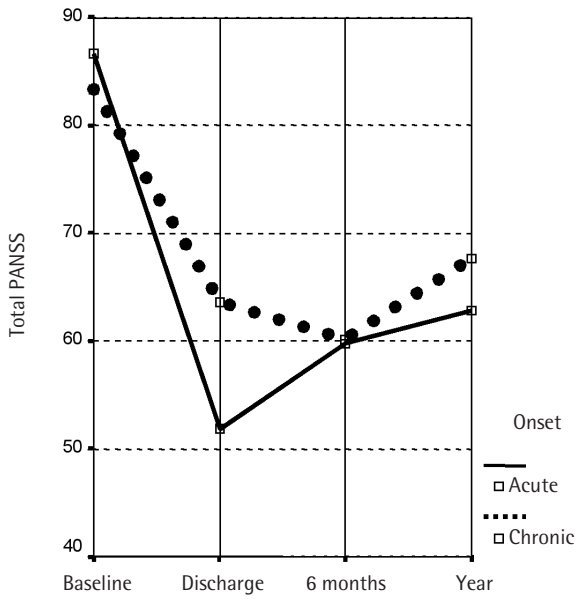

Figure 1 *Evolution of total PANSS in relationship with disease onset type. In the following chart, the evolution of the PANSS score in the different evaluations is shown, dividing the patients into two groups, those with acute disease onset (< 6 months) and those who have chronic disease onset (> 6 months). Those with acute onset have lower scores than those who suffered chronic onset, in spite of beginning with larger scores.*

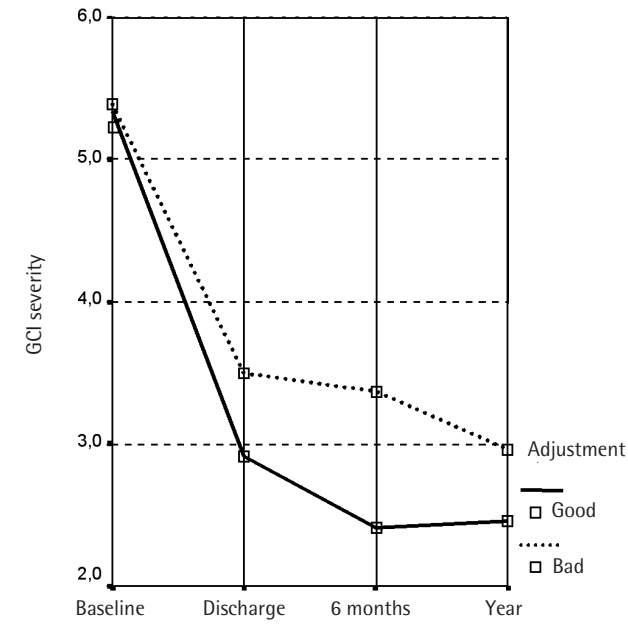

Figure 2 *Premorbid adjustment (Canon-Spoor) and disease course (CGI). In figure 2, the evolution of the CGI scale score when we divide the patients based on premorbid adjustment is observed. Thus, those with a previous better adjustment have lower score on this scale.*

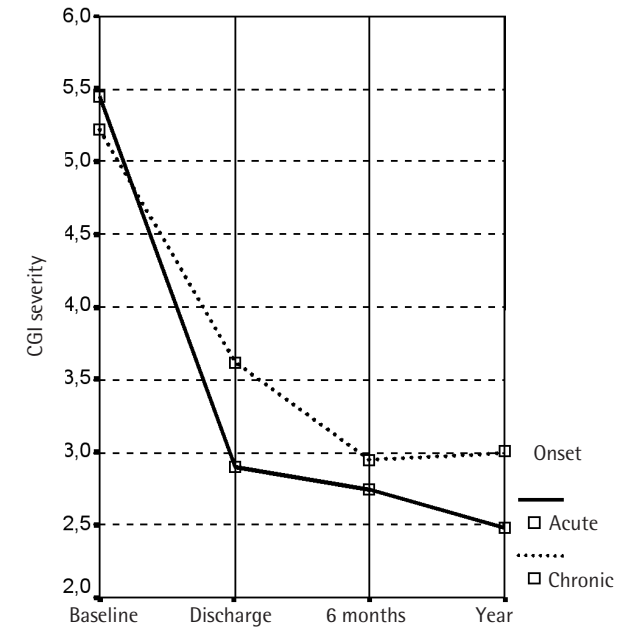

Figure 3 *Type of onset and disease course (CGI). In figure 3, the evolution of the CGI scale based on type of disease onset is shown. Patients with acute onset of it obtain lower scores on this scale.*

DUP and premorbid adjustment

Pearson's bivariate correlation coefficients between premorbid adjustment in its different subscales and DUP are seen in table 4. In general, the most prolonged DUP corresponds to greater score on the premorbid adjustment scales, indicating worse adjustment. These correlations are statistically significant ($p < 0.05$) with all the Cannon Spoor subscales, exceeding values of 0.30 with the adjustment subscales in early or late adolescence.

Very prolonged DUP

The relationship between very prolonged DUP (> 1 year) and less prolonged DUP (< 1 year) and disease course was evaluated. There was a majority of patients with DUP > 1 year (n = 52; 59.8 %). A weak association (not statistically significant) was observed between DUP > 1 year and all the PANSS scales at baseline. At 6 months, this difference was maintained, all the subscales except for positive symptoms reaching statistical significance, but these differences disappeared at 12 months. Thus, we could deduce that DUP > 1 year in our study was not associated with course or average score of the PANSS scale during the study.

A statistically significant association is observed between DUP > 1 year and worse premorbid adjustment, evaluated with the Cannon-Spoor scale and the Phillips adjustment scale. Those patients with very prolonged DUP had worse premorbid adjustment.

Table 4 Bivariante Pearson correlatons between premorbid adjustment and DUP subscales

Correlations	Time of symptoms without treatment
Time of symptoms without treatment	
Pearson correlation	1
Sig. (bilateral)	0
N	87
Total score (childhood)	
Pearson correlation	0.279
Sig. (bilateral)	0.009
N	87
Total score (early A.)	
Pearson correlation	0.333
Sig. (bilateral)	0.002
N	87
Total score (late A.)	
Pearson correlation	0.321
Sig. (bilateral)	0.002
N	87
Total score (adult age)	
Pearson correlation	0.232
Sig. (bilateral)	0.044
N	76
Total score (general)	
Pearson correlation	0.291
Sig. (bilateral)	0.007
N	86

*Correlation is significant at 0.01 level (bilateral). **Correlation is significant at 0.05 level (bilateral). DUP: duration of intreated psychosis.

DISCUSSION

DUP is important because during recent years, it has been affirmed that the disease prognosis becomes worse during the untreated period. Some authors would defend the existence of an active pathological process during the psychotic episode that can be decreased with antipsychotics[12,13]. The alteration arising from an untreated disease period would contribute to increasing social and psychological morbidity of the patient[14].

Besides this statement, the first psychotic episode is invariably associated to fear, depression and demoralization as well as generally producing an alteration of the productive life and sometimes deterioration of the social support network. If we consider that the episode is largely produced in the cases of late adolescence, period that determines the individual's occupational and social life adaptation, the harm produced by the disease in this period may be even more dramatic. Furthermore, the fact that rehabilitation in individuals with established schizophrenia produces limited benefit[15]) arouses an interest to approach the disease even before its onset.

It is especially interesting to identify the prognostic factors that may be modified by therapeutic or preventive interventions. In the different studies conducted in first psychotic episode patients, an alarmingly long interval between disease onset and initiation of treatment has been described. In our study, mean DUP reaches 560 days (SD: 851 days), it being similar to that described in other studies done previously in these types of patients[16,17]. Programs that try to reduce DUP have been initiated, this reduction being associated to the decrease of the disease severity[16].

On the other hand, it has also been defended that prolonged DUP could be related with clinical, social or demographic factors that delay identification of the disease, thus contributing to a worse prognosis[18]. Based on this, we divided our sample into two groups (prolonged DUP > 1 year vs DUP < 1 year). We observed a non-statistically significant correlation between the positive, negative symptoms and

total score of the PANSS in the baseline evaluation in the prolonged DUP group. At 6 months, a statistically significant association was seen in all the scales and the DUP > 1 year, except in that of the positive symptoms. This suggests that patients with a longer DUP would have a higher score on the negative subscale, these types of symptoms generally being less outstanding that the positive ones when treatment seeking is begun and they respond to antipsychotic treatment more slowly. However, at one year, these differences disappear. It can be stated that although the psychosis symptoms may be universal, the factors related with individual, familial, social influence and the social services may influence treatment seeking according to social context[19].

In our sample, we can see how the DUP was not significantly associated to the clinical prognosis during the first year. Although a weak correlation was initially observed between DUP and positive and negative symptoms of the PANSS in the baseline evaluation, when a repeated measures analysis of variance is applied, we find that the course of the positive and negative symptoms of the PANSS is not associated with the duration of untreated psychosis.

However, other studies have found evidence of a relationship between DUP and the final disease prognosis[7,11, 13,20-23]. In recent articles the association of DUP with the course of the positive symptoms at one year[24] and with the course of negative symptoms[25] has been described. Even when other possible prognostic factors were controlled, including premorbid functioning and gender, the DUP is a strong predictor of prognosis.

The association between a longer DUP and greater rate of recurrences has also been defined. Furthermore, retrospective studies have found that prolonged DUP may predict worse occupational prognosis at three years[26].

What is true is that there are also many references with similar results to that of our sample in which the DUP is not a prognostic factor, even when the follow-up period is longer[3,27,28,29].

One of the reasons of the negativeness of our results may be the relatively short follow-up period of one year. However, few studies have investigated the association of DUP and the disease prognosis beyond 5 years. In the study conducted by Lo and Lo[30], a study was done with 133 patients with schizophrenia for 10 years, demonstrating that a lower DUP before receiving the first treatment was associated significantly to a lower rate of recurrences.

Although it goes beyond the purpose of this article, we want to state that some authors have tried to find possible confounding factors that would act in the DUP - prognostic factor relationship. Thus, prolonged DUP has been related with worse social relationships, suggesting that treatment delay produces a social toxic effect or that those patients with poorer social relationships come to treatment later. It is interesting to stress that premorbid adjustment level in the social domain does not seem to influence social relationships when an episode occurs. This would reflect that this effect of DUP on social relationships is not affected by premorbid adjustment[31].

Poor social or occupational functioning in adolescence and in the year prior to initiation of treatment as the unclear onset of psychosis and presence of negative symptoms have been related with prolonged DUP[1 2,32].

The association between prolonged DUP and other prognostic factors that associate later treatment seeking such as familial psychiatric background, poor premorbid adjustment and low education level has been described[18]. Thus, association between duration of untreated psychosis and disease prognosis could be conditioned by the factors that delay treatment seeking and that are also factors having poor prognosis. In 2001, Verdoux[10] found that the strength of the association between the continuous course of the psychosis and duration of untreated psychosis is reduced after adjustment for premorbid function in the year prior to hospitalization. It was also seen to be decreased after adjustment for disease severity and intensity of the negative symptoms was also decreased. The explanation for this fact was that poor premorbid adjustment is a factor that is independently associated to DUP and poor prognosis, without a direct causal relationship between the last two variables. If this hypothesis proposed by Verdoux is certain, the strategies aimed at reducing the DUP would not have an impact on the disease course. Another hypothesis would suggest that the subjects with poor premorbid function would be less prone to seek treatment early. Consequently, there would be a greater risk of suffering a chronic course. Partly, DUP would measure the relationship between premorbid adjustment and prognosis. If this hypothesis is true, reducing DUP would contribute to decreasing the risk of non-remission of the disease. In our study, a statistically significant relationship is observed between prolonged DUP and worse premorbid adjustment. This relationship is more outstanding in the patient group having higher DUP at one year. That is, patients with worse adjustment are those who receive treatment later.

Some studies have associated very prolonged DUP with increase of alteration in adaptative social function[33] and with severity of negative symptoms. There does not seem to be an association between prolonged DUP in our sample and severity of negative symptoms.

In some cases, gender has also been associated with prolonged DUP and it has been described that men have a higher DUP than women[9]. Furthermore, in our sample, we found a substantially higher average DUP in men than in women, although these differences are not statistically significant. However, there are other studies[6] in which no association between gender and DUP is described.

Considering that some of the recent studies do not relate DUP with short term prognosis and that the arguments in favor of the association with poor prognosis do not prove that early identification is the reason for better prognosis in the cases treated early because it may be a screening effect, the role of DUP as a prognostic variable continues to be debatable. It is likely that the cases that have a better prognosis are precisely those that are detected earlier. It is difficult to prove that early detection has been the factor that has improved prognosis most in relationship with the best treatment in these studies.

One of the prognostic factors that appears to be bond undoubtedly to good prognosis in the first psychotic episodes is good premorbid adjustment[21]. This finding has also been confirmed in our study, a relationship between better premorbid adjustment (Canon-Spoor) and better evolution according to the CGI and PANSS scales being found.

It seems to be clear that possible confounding factors must be considered to distinguish the DUP-disease prognosis relationship. It has been suggested that the only way to finally clarify this relationship would be a randomized clinical trial study (35), with the clear ethical limitations that this means.

The association between prolonged DUP and worse prognosis may be explained in relationship to the different schizophrenia subtypes[36]. There is a group of patients with worse inherent prognosis that would cause delay in the detection of the disease. This type of disease would occur with a greater number of negative symptoms, fewer positive symptoms and limited disruption of social behavior. In support of this hypothesis, articles have been published that describe a prolonged DUP and higher scores for negative symptoms in patients with a first psychotic episode in their first hospital admission[37]. Thus, there would be a group of worse prognosis in which a later diagnosis would occur, either due to possible lack of insight and rejection of treatment or because the symptoms or behavior changes are not especially clear in the social context in which the patient functions. In our sample, the possible relationship between prolonged DUP and course of negative symptoms on the PANSS scale was studied without observing a clear association. However, when the analysis was conducted with the dichotomic criterion of the sample (DUP ≥ or < 1 year), a statistically significant relationship was found in the subscales of negative symptoms and general psychopathology and not with the subscale for the positive symptoms at 6 months. In the baseline evaluation, only a weak association with all the PANSS subscales was found. This relationship disappeared in the one year evaluation. Considering that the positive symptoms respond early to medication and the negative ones are generally more treatment resistant, it could be thought that this lack of association at one year would occur due to improvement of negative symptoms.

Another possible explanation is that the social variables associated with worse prognosis could delay detection or diagnosis of the disease. However, it has not been possible to confirm this hypothesis in all the studies conducted. Thus Haas et al.[38] found that premorbid function of individuals who have not received antipsychotics at one year or more after the first episode was superior to that of those who had received the medication before this.

Among the limitations of our study, we find the fact that the duration of untreated psychosis was calculated retrospectively from the information supplied by the patients and their family. On the other hand, the sample included patients with a first psychotic episode, but with heterogeneous diagnoses. We should remember that the different diagnostic groups were not compared to distinguish the effect that the diagnosis could produce in the sample and the possible effect of the different treatments in the final prognosis. Furthermore, data of the patients who refused to participate in the study were not collected, and this group could have had worse prognosis, thus altering their final results.

There is the possibility that the statistical power of the sample is insufficient to distinguish the effect that relates DUP with other prognostic factors.

As positive aspects, we mention that the study presents a patient group that is representative of the area who are affected by a first psychotic episode belong followed-up prospectively for one year.

CONCLUSIONS

What is certain is that in spite of the many studies existing in the current literature in this regards, it has not been possible to conclude the final relationship of DUP in the prognosis of psychotic disease. Our study shows one more piece of evidence in favor of the independence of the final prognosis and duration of untreated psychosis. It does not describe an association of prolonged DUP and the different prognostic scales used in the baseline time, at 6 and 12 months. As has been previously published, a statistically significant relationship of premorbid adjustment with disease course is observed, so that good premorbid adjustment in childhood and in adolescence would correlate with better disease course.

More studies are needed along the same line in patients affected by a first psychotic episode that demonstrate different advantages over chronic patients and that may be followed-up longitudinally.

REFERENCES

1. Johannessen JO, Larsen TK, MCG Lashan T. Duration of untreated psychosis: an important target for intervention in schizophrenia? Nord J Psychiatry 1999;53:275–83.

2. Larsen TK, MCG Lashan, Moe LC. First episode schizophrenia. I. Early-course parameters. Schizophr Bull 1996;22:241-56.
3. Barnes TRE, Hutton SB, Chapman MJ, Mutsatsa S, Puri BK, Joyce EM. West London first-episode study of schizophrenia: clinical correlates of duration of untreated psychosis. Br J Psychiatry 2000;177:207-11.
4. Waddington JL, Youssef HA, Kinsella A. Sequential cross-sectional and 10 years prospective study of severe negative symptoms in relation to duration of initially untreated psychosis in chronic schizophrenia. Psychol Med 1995;25:849-57.
5. Edwards J, Maude D, McGorry PD, Harrigan SM, Coks JT. Prolonged recovery in first episode psychosis. Br J Psychiatry 1998; 172(Suppl. 33):107-16.
6. Drake RJ, Haley CJ, Akhtar S, Lewis SW. Causes and consequences of duration of untreated psychosis in schizophrenia. Br J Psychiatry 2000;117;511-5.
7. McGorry PD, Edwards J, Mihalopoulos C, Harrigan SM, Jackson HJ. EPPICS: an evolving system of early detection and optimal management. Schizophr Bull 1996;22:305-26.
8. Birchwood M, Cochrane R, Macm Illan F, Copestake S, Kucharska J, Caross M. The influence of ethnicity and family structure on relapse in first-episode schizophrenia. Br J Psychiatry 1992; 161:783-90.
9. Loebel AD, Lieberman JA, Alvir JMJ, Mayerhoff DI, Geisler SH, Szymanski SR. Duration of psycosis and outcome in first-episode schizophrenia. Am J Psychiatry 1992;149:1183-8.
10. Verdoux H, Liraud F, Bergey C, Assens F, Abalan F, Van Os J. Is the association between duration of untreated psychosis and outcome confounded? A two year follow-up study of first-admitted patients. Schizophr Res 2001;49:231-241.
11. Carbone S, Harrigan S, McGorry PD, Curry C, Elkins K. Duration of untreated psychosis and 12-month outcome in first-episode psychosis: impact of treatment approach. Acta Psychiatr Scand 1999;100:96-104.
12. Waddington JL, Buckley PF, Scully PJ, et al. Course of psychopathology, cognition and neurobiological abnormality in schizophrenia: developmental origins and amelioration by antipsychotics? J Psychiatric Res 1998;32:179-89.
13. Wyatt RJ. Neuroleptics and the natural course of schizophrenia. Schizophr Bull 1991;17:325-51.
14. McGlashan TH. Early detection and intervention of schizophrenia: rationale and research. B J Psychiatry 1998;172(Suppl. 33): 3-6.
15. Borns BJ, Santos AB. Assertive community treatment: an update of randomized trials. Psychiatr Serv 1995;46:669-75.
16. McGlashan TH. Duration of untreated psychosis in first episode schizophrenia: marker or determinant of course? Biol Psychiatry 1999;899-907.
17. Kalla O, Aaltonen J, Wahlström J, Lehtinen V, García Cabeza I, González de Chávez M. Duration of untreated psychosis and its correlates in first episode psychosis in Finland and Spain. Acta Psychiatr Scand 2002;106:265-75.
18. Verdoux H, Bergey C, Assens F, Abalan F, Gonzales B, Pavillac P et al. Prediction of duration of psychosis before first admission. Eur Psychiatry 1998;13:346-52.
19. Vaglum P. Early detection and intervention in schizophrenia. Schizophr Bull 1996;22:347-52.
20. Wyatt RJ, Henter I. Rationale for the study of early intervention. Schizophr Res 2001;51:69-76.
21. Larsen TK, Moe LC, Vibe-Hansen L, Johannenssen JO. Premorbid functioning versus duration of untreated psychosis in 1 year outcome in first episode psychosis. Schizophr Res 2000;45:1–9.
22. Malla AK, Norman RM, Manchanda R, et al. One year outcome in first episode psychosis: influence of DUP and other predictors. Schizophr Res 2002;54:231-42.
23. Harrigan SM, McGorry PD, Krstev H. Does treatment delay in first episode psychosis really matter? Psychol Med 2003;33;97-110.
24. Addington J, van Mastrigt S, Addington D. Duration of untreated psychosis: impact on 2 year outcome. Psychol Med 2004; 34;277-84.
25. Edwards J, Harrigan S, McGorry P, Amminger PG. DUP and enduring positive/negative symptoms in first episode schizophrenia. Psychol Med 2002;32;563-4.
26. Inoue K, Nakajima T, Kato N. A longitudinal study of schizophrenia in adolescence. The one to three year outcome. Jpn J Psychiatry Neurol 1986;40:143-51.
27. Ho BC, Andreasen NC, Flaum M et al. Untreated initial psychosis: its relation to quality of live and symptom remission in first episode schizophrenia. Am J Psychiatry 2000;157:808-15.
28. Craig TJ, Bromet EJ, Fennig S, et al. Is there an association between duration of untreated psychosis and 24 month clinical outcome in a first admission series? Am J Psychiatry 2000;157: 60-6.
29. Wiersma D, Nienhuls FJ, Slooff CJ, Giel R. Natural course of schizophrenic disorders: a 15 year follow-up of a Dutch incidence cohort. Schizophr Bull 1998;24:75-85.
30. Lo WH, Lo T. A ten year follow-up study of Chinese schizophrenics in Hong Kong. Br J Psychiatry 1977;131:63-6.
31. Malla AK, Norman RM, McLean TS, McDonald C, McIntosh E, Dean-Lashley F, et al. Determinants of quality of life in first episode psychosis. Acta Psychiatr Scand 2004;109:46-54.
32. Larsen TK, Johannessen JO, Opjordsmoen S. First episode schizophrenia with long duration of untreated psychosis. Br J Psychiatry 1998;172(Suppl. 33):45-52.
33. Quinn J, Moran M, Lane A, Kinsella A, Waddington J. Long-term adaptative life functioning in relation to initiation of treatment with antipsychotics over the life time trajectory of schizophrenia. Biol Psychiatry 2000;48:163-6.
34. Meagher D, Quinn J, Kinsella A, Mullaney J, Waddington J. Relationship of the factor structure of psychopathology in schizophrenia to the timing of initial intervention with antipsychotics. Schizophr Res 2001;50:95-103.
35. McGorry PD. Evaluating the importance of reducing the duration of untreated psychosis. Aust N Z J Psychiatry 2000;34 (Suppl.):145-9.
36. Crow TJ, MacMillan JF, Johnson AL, et al. Northwick Park study of first episodes of schizophrenia. II. A randomised controlled trial of prophylactic neuroleptic treatment. Br J Psychiatry 1986; 148:120-7.
37. Binder J, Albus M, Hubmann W, et al. Neuropsychological impairment and psychopathology in first-episode schizophrenic patients related to the early course of illness. Eur Arch Psychiatry Clin Neurosci 1998;248;70-7.
38. Haas GL, Garratt LS, Sweeny JA. Delay to first antipsychotic medication in schizophrenia: impact on symptomatology and clinical course of illness. J Psychiatric Res 1998;32:151-9.