

Original Article

Relationship between Duration of Untreated Psychosis (DUP) and the One-Year Prognosis among Patients with First-Episode Schizophrenia

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OBJECTIVE: A number of reports have been published concerning the relationship between the duration of untreated psychosis (DUP) and the prognosis after treatment in patients with first-episode schizophrenia. However, many of these reports are based on analysis of patients hospitalized for the first time. The present study was undertaken to investigate the relationship between DUP and the one-year prognosis among the patients paying their first visit to the Outpatient Psychiatric Clinic of our hospital.

METHOD: Fifty-six patients diagnosed as having schizophrenia according to ICD-10 F20 were evaluated clinically using the Brief Psychiatric Rating Scale (BPRS) and the Global Assessment of Functioning (GAF) during the first visit and at a visit made one year later.

RESULTS: The percent improvement in the BPRS and GAF scores were greater in the patients with a shorter DUP. These results suggest that the DUP may serve as an independent predictor of the percent improvement in the BPRS and GAF scores. The percent improvement in both the BPRS score and GAF scores was significantly greater in the short DUP group (< 7 months) than in the long DUP group (> 7 months).

CONCLUSION: The one-year prognosis was better in the patients with a shorter DUP. The results additionally indicate that DUP may serve as an independent predictor of the one-year prognosis in patients with first-episode schizophrenia. The DUP was also shown to be significantly correlated with the one-year prognosis.

(Key words: Duration of untreated psychosis, First episode, Outpatients, Prognosis, Schizophrenia)

I. Introduction

The main topics of previous studies conducted on the early detection of schizophrenia and early intervention for the disease may be roughly divided into two groups. One pertains to research on the precursor symptoms of schizophrenia, for the purpose of primary prophylaxis or early secondary prophylaxis of the disease.

The other group of research topics pertains to secondary prophylaxis, i.e., research on the relationship between the prognosis after treatment and the duration of untreated psychosis (DUP), a concept primarily highlighted since the 1990s in Western countries. DUP refers to the length of time from the appear-

ance of positive symptoms or common symptoms to the start of psychiatric treatment.

In Japan, Mizuno et al.¹⁾ and Murakami et al.²⁾ reported similar data on DUP to those reported from Western countries. Very few reports have been published from Japan concerning the efficacy of systematic interventions, focusing on the prodromal symptoms of schizophrenia, or concerning the relationship between DUP and the outcome of treatment. In relation to research on the prodromal symptoms of schizophrenia, data have been increasingly accumulated concerning the risk-benefit profiles of pre-onset interventions that may justify such intervention, although the research data collected to date are still insufficient to justify pre-onset interventions in routine clinical practice. In view of this situation and the above-mentioned ethical problems, it is still difficult at present for psychiatrists to practice pre-onset interventions for schizophrenia in Japan, where research on this topic is still not extensive. Furthermore, many of the reports published to date concerning the relationship between DUP and the treatment outcome have only dealt with patients during their first hospital stay. According to our literature search, there are only a few reports of studies covering outpatients as well. Furthermore, even in this small group of reports including outpatients in their study population, either the major emphasis was on patients during their first hospital stay, or the number of patients evaluated was quite small^{3),4),5)}. The present study was undertaken against this background, to investigate the relationship between the DUP and the prognosis after treatment of patients diagnosed to have schizophrenia at their first visit to the Department of Psychiatry of Jichi Medical University Hospital.

II. Subjects and Methods

A. Subjects

Of the patients of both sexes who made the first contact with the Outpatient Psychiatric Clinic of the Jichi Medical School Hospital between April 1, 2004, and October 31, 2005, those diagnosed to have “F20: schizophrenia” according to ICD-10 were eligible for this study.

B. Methods

The physicians in charge of new outpatients at our hospital confirmed that each of the patients satisfied the criteria for first contact and, if a patient was diagnosed as a case of “F20: schizophrenia” according to ICD-10, the patient and/or his/her guardian was informed of the design of this study. If consent for the study was obtained, one of the physicians (the authors of this paper) in charge of the investigation entered the following information in the DUP survey form: date of first contact, ID and the name, date of birth, age and sex of the patient.

Thereafter, the patient was interviewed in the presence of some attendants (**family members or others**) to collect information about the time of first appearance of symptoms (DUP), family history, education level, occupational career, and marital status, and then evaluated clinically using the Brief Psychiatric Rating Scale (BPRS) and the Global Assessment of Functioning (GAF) scale.

One year after the first contact, the same physician in charge of the investigation repeated the interview and clinical evaluation of the patient using BPRS and the GAF scale, in the same manner as at the first contact. The information collected from the second interview/evaluation was entered in the same survey form as that used at the first interview/evaluation, while taking care to carefully separate the information entered at the first contact and the visit a year after. In cases where a personal interview was difficult, the interview/evaluation was performed by the physician in charge of the investigation over the

telephone. The dropouts and refusers were excluded from the final evaluation.

The frequency of hospital visits, drug dose levels, etc., varied among the finally evaluated subjects requiring treatment. All of these subjects underwent periodic examinations by their attending physicians, and adequate treatment.

Upon completion of the second survey, the relationship between the DUP and the prognosis of the patients with schizophrenia was evaluated by analyzing the correlation between the DUP and the percent improvement over one year in the scores on the BPRS and GAF scales, i.e., Δ BPRS (%) and Δ GAF (%). **Thus, the secondary prophylactic efficacy against further episodes of schizophrenia of early detection and treatment was evaluated.** All the analyses and tests were performed using the statistical software Dr. SPSS II for Windows (Japanese version). In all the tests, $P < 0.05$ (both-sided) was considered to denote statistical significance.

All the data of the subjects were treated in an anonymous way. The personal computers used for storage and analysis of the data were kept out of the network during the data analysis. Data were saved on floppy discs to avoid hacking by outsiders.

The study was carried out with the authorization of the Research Ethics Committee and Bioethics Committee of the Jichi Medical University (Approval No. Extra 03-31).

III. Results

A. Data collection (Table 1)

Table 1 Data collection (first contact: 1602 patients)

Subjects	79 cases
- Refusers	6 cases
- Dropouts	17 cases
Finally evaluated subjects	56 cases (20 males and 36 females)*
*Interview/evaluation over telephone: 3 males and 5 females	

A total of 1602 patients made first contact with our department between April 1, 2004, and October 31, 2005, and 79 of these were enrolled as the study subjects for this study. Of the 79 subjects, 6 refused consent for the second interview/evaluation, and 17 discontinued visiting the hospital at their own discretion, without consulting their attending physicians and were therefore labeled as dropouts. Thus, the number of finally evaluated subjects was 56 (20 males and 36 females). Of these 56 finally evaluated subjects, 3 males and 5 females were interviewed /evaluated over the telephone at one year after the first contact.

B. DUP, the examination findings at the first contact and history of hospitalization (Table 2-1, 2)

Table 2-1 DUP

	Total (N = 56)	Males (N = 20)	Females (N = 36)	P ^{§)}
Median (months)	7	3.5	9	N.S.
Mean (months)	23.0	31.1	18.4	
S.D. (months)	36.5	44.2	31.3	

^{§)} Mann-Whitney's U-test

Table 2-2. Examination findings at the first contact and history of hospitalization

	Total (N = 56)	Males (N = 20)	Females (N = 36)	P ^{§)}
	Median (S.D.)	Median (S.D.)	Median (S.D.)	
Age at first contact	31 (12.4)	29.5 (9.7)	33.5 (13.7)	N.S.
Age at disease onset	28.5 (12.5)	27.5 (9.3)	30 (13.9)	N.S.
Length of education(years)	12 (2.1)	12 (2.1)	12 (2.2)	N.S.
	(%)	(%)	(%)	P ^{§ §)}
Unmarried (Divorced)	38 (67.9)	17 (85.0)	21 (58.3)	N.S.
Married	18 (32.1)	3 (15.0)	15 (41.7)	
Hospitalization history				
Present	16 (28.6)	4 (20.0)	12 (33.3)	N.S.
Absent	40 (71.4)	16 (80.0)	24 (66.7)	

^{§)} Mann-Whitney's U-test, ^{§ §)} Fisher's exact test

There were no significant differences in all investigation items.

C. BPRS and GAF scores at the first contact and at one year after the first contact and the percent improvement of the scores over 1 year (Table 3)

Table 3 BPRS and GAF scores at first contact, at one year after the first contact and the percent improvement of the scores over 1 year

	Total (N = 56)	Males (N = 20)	Females (N = 36)	P ^{§)}
	Median (S.D.)	Median (S.D.)	Median (S.D.)	
BPRS-first contact	49 (10.9)	49.5 (7.8)	47.5(12.3)	N.S.
GAF-first contact	41 (10.0)	43 (12.8)	41 (8.3)	N.S.
BPRS-one year	25 (8.4)	27 (6.9)	25 (9.3)	N.S.
GAF-one year	60 (12.7)	57.5(17.1)	60.5 (9.7)	N.S.
ΔBPRS(%) [†]	72.9(22.8)	72.1(24.6)	74.1(22.1)	N.S.
ΔGAF(%) ^{††)}	32.3(21.0)	27.7(26.0)	33.9(17.9)	N.S.

[†]ΔBPRS(%) = (BPRS score at fist contact – BPRS score at 1 year) / (BPRS score at first contact – 18) × 100

^{††}ΔGAF(%) = (GAF score at one year – GAF score at first contact) / (100 – GAF score at first contact) × 100

^{§)} Mann-Whitney's U-test

There were no significant differences in all investigation items.

D. Correlations among variables (Table 4)

Table 4. Correlations among variables (Spearman's rank correlation, N=56)

	DUP	Age upon Disease onset	Educational career	BPRS first-conta	GAF first-conta	ΔBPRS (%) ^{†)}	ΔGAF (%) ^{††)}
DUP	—	-.134	-.194	-.283*	.289*	-.634**	-.484**
Age upon Disease onset		—	-.019	.049	-.124	-.017	.037
Educational career			—	-.193	.026	.284*	.332*
BPRS first contact				—	-.537**	-.076	-.055
GAF first contact					—	.004	-.068
ΔBPRS (%) ^{†)}						—	.865**
ΔGAF (%) ^{††)}							—

[†]ΔBPRS (%) = (BPRS score at fist contact – BPRS score at 1 year) / (BPRS score at first contact – 18) × 100

^{††}ΔGAF (%) = (GAF score at one year – GAF score at first contact) / (100 – GAF score at first contact) × 100

*p < 0.05, **p < 0.01

A weak negative correlation between the DUP and the BPRS score at first contact ($r = -0.283$, $p < 0.05$), and a weak positive correlation between the DUP and the GAF score at first contact ($r = 0.289$, $p < 0.05$) were observed. Negative correlations between the DUP and the percent improvement in the BPRS score and percent improvement in the GAF score were also noted ($r = -0.634$, $r = -0.484$, $p < 0.01$). **Also, weak positive correlations were found between the length of education and the percent improvement in the BPRS score and percent improvement in the GAF scores** ($r = 0.284$, $r = 0.332$, $p < 0.05$).

In addition, a negative correlation was noted between the BPRS score at first contact and the GAF score at first contact ($r = -0.537$, $p < 0.01$). A strong positive correlation was noted between the percent improvement in the BPRS score and the percent improvement in the GAF score ($r = 0.865$, $p < 0.01$).

E. Multiple regression analysis (1) (Table 5)

Table 5. Results of multiple regression analysis (1)

Independent variable	Dependent variable				
	Δ BPRS(%) [†]				
	Partial regression coefficient	Standard error	Standard partial Regression coefficient	t	P
DUP	-.348	.074	-.557	-4.721	***
Age at disease onset	-.031	.206	-.017	-.152	N.S.
Length of education	1.638	1.249	.154	1.311	N.S.
BPRS first contact	.394	.250	-.188	-1.579	N.S.

Multiple correlation coefficient (R) = .600 Coefficient of determination (R^2) = .360

$F_{(4,51)} = 7.175^{***}$

$\dagger \Delta$ BPRS(%) = (BPRS score at fist contact – BPRS score at 1 year) / (BPRS score at first contact – 18) \times 100 ***p < .001

The results of the analysis revealed that DUP was the only factor determining the percent improvement in the BPRS score over 1 year ($t = -4.721$, $p < 0.001$).

F. Multiple regression analysis (2) (Table 6)

Table 6. Results of multiple regression analysis (2)

Independent variable	Dependent variable				
	Δ GAF (%) ^{††}				
	Partial regression coefficient	Standard error	Standard partial Regression coefficient	t	P
DUP	-.228	.073	-.396	-3.111	**
Age at disease onset	-.069	.208	-.041	-.331	N.S.
Length of education	2.104	1.229	.215	1.712	N.S.
GAF first contact	-.051	.263	-.025	.195	N.S.
Multiple correlation coefficient (R) = .478			Coefficient of determination (R ²) = .229		
F _(4,51) = 3.785***					
^{††} Δ GAF(%) = (GAF score at 1 year – GAF score at first contact) / (100 – GAF score at first contact) × 100 **p < .01					

The results of the analysis revealed that DUP was the only factor determining the percent improvement in the GAF score over 1 year (t = -3.111, p < 0.01).

G. Comparison of characteristics between the short DUP group and long DUP group (Table 7)

Table 7. Comparison between the short DUP group and long DUP group

	Short DUP group (<7 months*)		Long DUP group (>7 months*)		P ^{§)}
	Mean	(S.D.)	Mean	(S.D.)	
BPRS-first contact	51	(9.9)	47	(11.5)	N.S.
GAF-first contact	38.5	(10.7)	45	(8.3)	*
BPRS-one year	21.5	(4.6)	28	(9.9)	**
GAF-one year	65	(13.1)	60	(12.0)	N.S.
Δ BPRS (%) [†]	87.9	(12.5)	59.5	(23.8)	***
Δ GAF (%) ^{††}	42.5	(19.3)	26.9	(19.3)	**

*7 months: median DUP in the present study

[†] Δ BPRS(%) = (BPRS score at fist contact – BPRS score at 1 year) / (BPRS score at first contact – 18) × 100

^{††} Δ GAF(%) = (GAF score at one year – GAF score at first contact) / (100 – GAF score at first contact) × 100

§) Mann-Whitney's U-test, *P < 0.05, **P < 0.01, ***P < 0.001

The median BPRS score at first contact differed little between the short DUP group (51) and the long DUP group (47), while the median BPRS score at one year after the first contact showed significantly greater improvement in the short DUP group (21.5) than in the long DUP group ($p < 0.01$). The median percent improvement of the BPRS score over one year was also significantly higher in the short DUP group (87.9) than in the long DUP group (59.5) ($p < 0.001$).

The median GAF score at first contact was significantly better in the long DUP group (45) than in the short DUP group (38.5) ($p < 0.05$), while the median GAF score at one year after the first contact differed little between the short DUP group (65) and long DUP group (60). The median percent improvement in the GAF score over one year was significantly higher in the short DUP group (42.5) than in the long DUP group (26.9) ($p < 0.01$).

IV. Discussion

In previous major studies in relation to the relevance of the DUP, the standard deviation of the DUP was large, with the mean DUP being about 1-2 years and median DUP being about 2-12 months^{6,7,8,9,10,11,12,13,14} (Table 8).

Table 8. DUP in previous studies

	n	Median (weeks)	Mean (weeks)	S.D.
Beiser et al. (1993)	72	8	56	148
Birchwood et al. (1992)	71		30	
Häfner et al. (1994)	165		109	
Haas and Sweeny (1992)	71		99	
Larsen et al. (1996)	43	26	114	173
Loebel et al. (1992)	70	39	52	82
Møller and Husby (2000)	18	18	32	35
McGorry et al. (1996)				
pre-EPPIC	200	30	227	714
post-EPPIC	147	52	175	385
Moscarelli et al. (1994)	20		76	92

In the present study, the mean DUP was 23.0 months and the median DUP was 7 months (S.D. 36.5 months). Thus, the values in the present study were approximately equal (the mean and S.D. were slightly larger) to those reported by previous major studies (Table 2-1).

In the present study, percent improvements in the BPRS and GAF scores over one year (Δ BPRS (%) and Δ GAF (%) in Table 3), which were used as the indicators of prognosis, were found to be correlated with the DUP ($r = -0.634$, $r = -0.484$, $p < 0.01$), and additionally showed a weak correlation with the length of education ($r = 0.284$, $r = 0.332$, $p < 0.05$), as shown in Table 4. Although the percent improvements in both the BRPS and GAF scores showed a weak correlation with the length of education, it is dif-

difficult to understand why the percent improvement in the BPRS score (a scale of psychiatric symptoms) would be directly associated with the length of education. In this connection, Gaite et al.¹⁵⁾ reported that the major factors determining the GAF score were clinical factors such as the BPRS score, duration (years) of mental health service utilization, and abuse of alcohol, although other factors associated with social and daily living functioning were also found to be significantly correlated with the GAF score. This explains how the length of education is correlated with the percent improvement in the GAF score.

A strong positive correlation was noted between percent improvement in the BPRS score and the percent improvement in the GAF score ($r = 0.86$, $p < 0.01$) over one year, as shown in Table 4. This can be interpreted as indicating that when alleviation of psychiatric symptoms to some extent is seen following initial therapy, the improvement in overall functioning can further accelerate the alleviation of psychiatric symptoms such as anxiety and tension. In any event, we may say that this strong correlation may have led to the secondary correlation between the length of education and the percent improvement in the BPRS score.

After determining these correlations among the variables, we conducted multiple regression analyses using the percent improvement in the BPRS score or that in the GAF score as the dependent variable. In both analyses, DUP was identified as the only factor possibly determining the dependent variable (Table 5 and 6).

The present study results revealed that the DUP was significantly correlated with the one-year prognosis and that it may serve as an independent predictor of the one-year prognosis. Furthermore, when the subjects were divided by the DUP into the short DUP group and long DUP with the cutoff level set at 7 months (median DUP in the present study), the median percent improvements in both the BPRS and GAF scores were significantly better in the short DUP group than in the long DUP group, confirming the significant correlation between the DUP and the one-year prognosis (Table 7).

A number of reports have been published concerning the relationship between DUP and the prognosis. Most of these reports are based on data obtained from patients hospitalized with first episode schizophrenia. Drake et al.⁴⁾ and Malla et al.⁵⁾ conducted surveys that also included outpatients, however, there were considerable limitations in the inclusion criteria used by them (e.g., the subjects were required to be participants in the treatment program designed by them). **Probably for this reason, most of the finally evaluated subjects in the study by Drake et al.⁴⁾ were inpatients (inpatients: 212; outpatients: 36).** Black et al.³⁾ conducted a survey including only outpatients with first-episode schizophrenia, however, the number of finally evaluated subjects was only 19. Furthermore, diverse scales were used as indicators of prognosis in these previous studies, without adoption of a uniform scale. Among these reports, the reports on the short-term prognosis (for up to about 3 years) by Harrigan et al.¹⁶⁾ and Larsen et al.¹⁷⁾, a report on the medium and long-term prognosis (over 3 years) by Harris et al.¹⁸⁾, etc., demonstrated a correlation between the DUP and the prognosis and the role of DUP as an independent factor determining the prognosis as assessed using the scores in the BPRS and GAF, similar to the approach used in the present study. Regarding the significance of the relationship between the DUP and prognosis, Black et al.³⁾, Hass et al.¹⁹⁾ and Ucock et al.²⁰⁾ reported that DUP is related to the short-term prognosis, reporting that the improvements in the BPRS and GAF (GAS) scores were better in the short DUP group, and Bottlender et al.²¹⁾ and Harris et al.¹⁸⁾ reported that the DUP is related to the medium and long-term prognosis, reporting that the improvement in the BPRS and GAF (GAS) scores were more marked in the short DUP

group at about 6-12 months or more after the start of treatment. On the other hand, some investigators such as Craig et al.²²⁾ reported no significant differences in the improvements of the BPRS and GAF scores depending on the DUP. In the study reported by Craig et al., Harrigan et al.¹⁶⁾ pointed out: "The patients studied by Craig et al. were managed at 12 facilities, and biases cannot be ruled out, not only in the drug therapy regimens used, but also in the overall services provided to them."

Unlike in many previous studies, the subjects were not confined to inpatients in the present study. Instead, all the patients with first-episode schizophrenia who made the first contact with our facility were eligible for this study, irrespective of their hospitalization status (inpatient/outpatient). The composition of the 56 finally evaluated subjects in this study differed significantly from that of previous studies in that the number of outpatients was 2.5 times that of inpatients; that is, of the 56 subjects, 16 had a history of hospitalization after the first contact and the remaining 40 remained outpatients after the first contact, as shown in Table 2-2. This feature of the present study suggests that the subjects of this study differed qualitatively from those of previous studies. The greater number of outpatients than inpatients suggests that possibility that the clinical symptoms of the subjects of this study were often mild, but on the other hand, there were many patients in whom the clinical symptoms were severe enough to necessitate hospitalization, but their favorable social environments (support of family members, etc.) allowed outpatient care. Notwithstanding, the results of this study also revealed a significant correlation between the DUP and the prognosis of the patients and the possible role of the DUP as an independent predictor of the prognosis, consistent with the results of previous studies, endorsing the significant role of DUP as an indicator of the prognosis in schizophrenia. This finding is thus a noteworthy finding.

However, unlike previous studies in which numerous scales have been used for the evaluation, we used only the BPRS and GAF in the present study. While we are aware that multi-faceted and detailed evaluation using many scales might be more desirable, we were forced to conduct the present study using the minimum necessary parameters because of the time constraint imposed by the study of outpatients.

V. Conclusion

In all first-contact patients with first-episode schizophrenia, we analyzed the relationship between the duration of untreated psychosis (DUP) and the one-year prognosis, using the scores in the BPRS and GAF as indicators of the prognosis. The results revealed that the one-year prognosis was significantly better in patients with a shorter DUP. In other words, the results indicated that the DUP may serve as an independent predictor of the one-year prognosis.

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初回エピソード統合失調症の精神病未治療期間 (Duration of untreated psychosis : DUP) と 1 年予後

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要 約

目的：初回エピソード統合失調症の精神病未治療期間 (Duration of untreated psychosis : DUP) と治療予後との関係はこれまでも多数報告されている。しかし、その報告のほとんどは初回入院患者を対象としている。今回われわれは、すべての外来初診患者を対象にして、DUP と 1 年後治療予後との関係を調査した。

方法：ICD-10 F20：統合失調症と診断された56名の初回エピソード患者らは初診時と1年後に簡易精神症状評価尺度 (Brief Psychiatric Rating Scale : BPRS) と全般的機能評価尺度 (Global Assessment of Functioning : GAF) で臨床評価をされた。結果：DUP が短いほど BPRS 改善率, GAF 改善率は良好であった。DUP は

BPRS 改善率, GAF 改善率に対して独立した予測因子である可能性が示唆された。短期 DUP 群 (<7ヶ月) は長期 DUP 群 (>7ヶ月) より BPRS 改善率, GAF 改善率が有意に良好であった。

結論：DUP が短いほど1年後治療予後は良好であった。DUP は1年後治療予後に対して他の予測因子の影響を受けない独立した予測因子である可能性が高いことが示された。DUP は1年後治療予後に対して有意性があることも確認された。

(キーワード：精神病未治療期間, 初回エピソード, 外来患者, 予後, 統合失調症)