Acta Med. Nagasaki 54: 59－66

Nagasaki Schizophrenia Study: Relationship Between Ultralong-term Outcome (after 28 years) and Duration of Untreated Psychosis

Hitoshi ICHINOSE,[1] Yoshibumi NAKANE,[2] Hideyuki NAKANE,[3] Hirohisa KINOSHITA,[4] Yasuyuki OHTA,[5] Sumihisa HONDA,[6] Hiroki OZAWA[1]

[1] Department of Neuropsychiatry, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

[2] Department of Neuropsychiatry, Dejima Clinic, Nagasaki, Japan

[3] Department of Occupational Therapy, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

[4] Nagasaki University Hospital, Department of Neuropsychiatry, Nagasaki, Japan

[5] Department of Rehabilitation, Nishikyusyu University, Saga, Japan

[6] Department of Public Health, Nagasaki University Graduate School of Biomedical Sciences, Nagasaki, Japan

Objective: Numerous studies have shown a relationship between the duration of untreated psychosis (DUP) in schizophrenia and short-term outcome. However, few studies have investigated the relationships between DUP and the medium-term and long-term outcomes. Furthermore, we are unaware of any reports regarding the relationship between DUP and the ultralong-term outcome. This study aimed to investigate the relationship between DUP and ultralong-term outcome at 28 years in patients with schizophrenia.

Method: Patients with schizophrenia completed an interview survey 28 years after their initial psychiatric examination during the period 1979-1980. It was possible to conduct the survey using suitable assessment scales in 31 patients in whom DUP was confirmed. These patients were divided into a short DUP group and a long DUP group on the basis of the median DUP, and the outcomes of these two groups were compared. Results: Longer DUP correlated significantly with poorer symptomatic outcome; degree of social adjustment; and, global functioning. Multiple linear regression analysis found no changes in these results even after controlling for various factors, including gender, age at onset, mode of onset, diagnostic subtype, and premorbid adjustment.

Conclusion: DUP adversely affected ultralong-term outcome of schizophrenia after 28 years. This finding supports the need to establish a system to enable early detection and appropriate intervention for patients with schizophrenia to reduce the risk of a deleterious outcome after more than 25 years.

ACTA MEDICA NAGASAKIENSIA 54: 59－66, 2009

Keywords: Schizophrenia; Ultralong-term outcome; Duration of untreated psychosis

Introduction

Numerous studies have shown an association between duration of untreated psychosis (DUP) in schizophrenia and short-term outcome. Many groups have demonstrated that clinical outcome worsens as DUP lengthens.[1-5] However, not all of these studies may have adequately dealt with potential confounders.[1,4,6,7] In addition, past studies have varied in terms of factors such as diagnostic criteria, the scope within which patients were recruited, and prospective vs. retrospective design. Moreover, most studies investigating the association of DUP with outcome have focused on short-term outcome. Some reports addressed the very short-term outcome, consisting of only several months,[8-12] whereas others have investigated the short-term outcome after 6 months or approximately 2 years.[13-24] Few studies have investigated the relationship of DUP to medium-term outcome (after approximately 5 years)[25-28] or the long-term outcome (after 10 years or more).[29-31] Our literature search found no studies with a follow-up period longer than 20 years. Early intervention for the first episode of psychosis is considered important,[32-35] and we therefore surmised it necessary to elucidate the significance of that finding in the long-term by surveying the outcome over an ultralong-term period. The long-term studies conducted to date have indicated an association between DUP and outcome of schizophrenia.[29-31] The present study thus aimed

Address correspondence: Hitoshi Ichinose, M.D., Department of Neuropsychiatry, Unit of Translational Medicine, Nagasaki University Graduate School of Biomedical Sciences, 1-7-1 Sakamoto, Nagasaki 852-8501, JAPAN
TEL: +81-(0)95-819-7293, FAX: +81-(0)95-819-7296, E-mail: hmwjr747@ybb.ne.jp

Received November 12, 2009; Accepted December 7, 2009

to validate the hypothesis that DUP affects outcome of schizophrenia even with an ultralong-term follow-up period of 28 years.

Materials and Methods

Background

This research was based on the WHO International Collaborative Study on Determinants of the Outcome of Severe Mental Disorders (DOSMeD Study) performed from January 1979 through December 1980 by the Department of Neuropsychiatry of Nagasaki University (hereinafter, the Nagasaki Center) in collaboration with the World Health Organization (WHO).[36,37] Preparation began in the second half of 1976, and the DOSMeD Study was then conducted by the WHO Collaborating Centers in various countries around the world. The Department of Neuropsychiatry of Nagasaki University is formally designated as a WHO Collaborating Center for Research and Training in Mental Health, and thus continued to participate in the research.

Study design

Participants were selected according to the following method. A 3-month pilot study was conducted from October 1978 to investigate the behavioral patterns of Nagasaki City residents with schizophrenia at the time of their initial medical examination. One of the objectives of the DOSMeD study was to investigate the incidence of schizophrenia. It was therefore necessary to enroll patients who had lived within a certain geographical area for a certain period of time, who had developed schizophrenia for the first time and who were examined at a medical institution for the first time in a drug-naive state. As a result, 30 medical institutions with psychiatry departments (18 private psychiatry hospitals, 5 private psychiatry clinics, 1 prefectural psychiatry hospital, 4 public general hospital psychiatry departments, and 2 health centers) were selected from within Nagasaki City and its environs.[36,37] This group of institutions was called the Case Finding Network (CFN). Patients presenting with psychosis for the first time at CFN institutions between January 1979 and December 1980 were screened for inclusion eligibility by research associates from the Nagasaki Center. Informed written consent for participation was obtained from the patient and his/her family prior to screening.

The inclusion criteria for the subjects were as follows. 1) Residence in Nagasaki City for at least 6 months during the year prior to the consultation. 2) Aged 15-54 at first consultation. 3) No prior consultation with a psychiatry department. 4) Absence of organic brain disorders and mental retardation, and no dependence on psychotropic substances, including alcohol. In addition, subjects had to satisfy the criteria for the specified psychotic symptoms and behavioral abnormalities shown below in (a) 1-5 and (b) 1-5.[38]

Patients need one of the following symptoms from (a) or (b).

(a) During the past year the patient had at least one of the following.
1. Hallucinations or pseudo hallucinations in any modality.
2. Delusions.
3. Marked thought and speech disorder (e.g., incoherence, irrelevance, thought blocking, neologisms, or incomprehensibility of speech).
4. Marked psychomotor disorder (e.g., negativism, mutism or stupor; catatonic excitement; constrained attitudes or unnatural postures maintained for long periods).
5. Emergence or marked exacerbation of bizarre and grossly inappropriate behavior (e.g., talking or giggling to self, acts incomprehensible to others, loss of social constraints).

(b) During the past year, patients had presented a definite change of personality and behavior with at least one of the following.
1. Marked reduction or loss of interest, initiative and drive, leading to severe deterioration of performance of usual activities and tasks.
2. Emergence or marked exacerbation of social withdrawal.
3. Severe excitement, purposeless destructiveness, or aggression.
4. Episodic or persistent state of overwhelming fear or severe anxiety.
5. Gross and persistent self-neglect.

A total of 107 patients (61 males, 46 females) met the criteria and were enrolled in the study. At the initial assessment, the subtype of schizophrenia was diagnosed in accordance with the International Classification of Diseases 9 (ICD-9).[39] Those diagnostic criteria were subsequently revised, and as a result re-classification was performed in 1994 on the basis of the ICD-10.[40] Patient follow-up was conducted at 1, 2, 5, 10, and 15 years.[36,41,42] As long as a participant continued to consult with the CFN referring institution, the usual treatment was continued at that institution. Participants were given complete discretion over any decision to change the consulting institution or drop out of the study. Follow-up outcome surveys performed after 5 and 10 years were conducted by the Nagasaki Center. Follow-up was completed for the following numbers (%) of participants, including those who had died: 2 years, 65 (60.7%); 5 years, 66 (61.6%); 10 years, 66 (61.6%); and, 15 years, 65 (60.7%). The numbers (%) of participants who had died at each follow-up were as follows: 2 years, 1, (0.9%); 5 years, 1 (0.9%); 10 years, 5 (4.7%); and, 15 years, 7 (6.5%). Therefore, approximately 40% of all participants dropped out of follow-up during the initial 1 to 2 years of the study.[36]

Ultralong-term follow-up interviews

We investigated the effect of DUP and other related factors on ultralong-term outcome (over 28 years from the start of treatment). Follow-up interviews were conducted over a 2-year period, from January 2007 through December 2008. The first step was to re-locate the participants who had been enrolled in the study. We started by explaining the nature and objectives of the study at a seminar of Nagasaki Prefecture psychiatrists that was attended by many psychiatric treatment staff from within Nagasaki Prefecture. In addition, Nagasaki Center psychiatrists visited each of the medical institutions in the CFN as well as psychiatric treatment organizations

at the periphery of the CFN and presented a thorough explanation of the nature and objectives of this ultralong-term outcome study, culminating with an earnest request for their cooperation. The institutions were asked if they were treating any of the original participants, and the contact addresses of those patients were thus newly determined. When it was elucidated that a previous participant was being treated at an institution, the consent of the patient's primary physician was obtained. A research associate (a psychiatrist) then contacted the patient and thoroughly explained the nature and objectives of the study. If informed written consent was obtained from the patient and his/her family to participate, the research associate conducted the outcome survey. This study was conducted in accordance with the Declaration of Helsinki; full informed consent was obtained, and careful attention was paid to ensuring confidentiality and anonymity to protect each patient's privacy. The Ethics Committee of Nagasaki University School of Medicine approved this study.

The instruments used for this ultralong-term outcome survey consisted of the Disability Assessment Schedule (DAS),[43] the Global Assessment Scale (GAS),[44] and the Clinical Global Impressions (CGI).[45] These instruments were used to assess characteristics such as psychiatric symptoms, degree of social adjustment, and global social functioning. The interview surveys were conducted by one psychiatrist who had undergone thorough training for each of these instruments.

In this study, DUP was determined using the Psychiatric and Personal History Schedule (PPHS),[38,42] which was described in 1979-1980, when the DOSMeD study was initiated. At that time, psychiatrists who had undergone thorough and uniform training for the PPHS were able to accurately elucidate the time of onset of schizophrenia by consultation with the patients and interviews with the families. Using that data, DUP was calculated as the time from disease onset until the start of treatment at a medical institution. In addition, information regarding the participant's gender, age at onset, mode of onset, and premorbid adjustment (i.e., during childhood and adolescence) was recorded in the PPHS. Jablensky's classification[38] was used to diagnose the mode of onset: acute was defined as manifestation of psychotic symptoms within 1 month after the initial marked behavioral change, while insidious was defined as gradual manifestation of psychotic symptoms more than 1 month after the initial marked behavioral change. Diagnosis based on the ICD-9 at the initial assessment was recorded in the Diagnostic and Prognostic Schedule (DPS).[38] At present, most studies employ the Premorbid Adjustment Scale (PAS)[46] or the Modified Premorbid Adjustment Scale (MPAS)[47] when investigating premorbid adjustment, but neither of those instruments had yet been established when patients were initially recruited for this study. However, as with the MPAS, accurate information regarding adjustment during childhood and adolescence were stated in the PPHS.

Subjects

DUP was confirmed in 97 (54 males, 43 females) of the 107 patients who were recruited at the start of the study.[42] For the present ultralong-term outcome survey, a search for all original participants was conducted, and the patients who were successfully traced were included.

The research associates who conducted this survey were blinded to the results of the follow-up surveys that had been conducted up to the 15-year point after the start of the DOSMeD study.

Statistical analysis

All statistical analyses were performed using SAS, version 9.2 (SAS Institute, Inc., Cary, NC). The chi-square test was used to compare baseline parameters between the patient group for which follow-up in the present survey was achieved and DUP had been confirmed and the patient group for which DUP had been confirmed but follow-up had not been achieved. The analyzed baseline parameters consisted of gender, mode of onset, diagnostic subtype (based on the ICD-9), and premorbid adjustment. Age at onset and DUP were analyzed using the Wilcoxon rank-sum test.

Many previous studies and reviews have reported that DUP has a large standard deviation and is extremely long for some patients. Considering these characteristics and in order to guarantee the validity of the present study, the median values for DUP were used for analysis. The participants were divided into two groups (the long-DUP group, >4 months; and the short-DUP group, ≤3 months) on the basis of the median DUP values, and then the Wilcoxon rank-sum test was used to compare outcome between these two groups. With the objective of examining whether DUP is an independent predictor of the ultralong-term outcome, Multiple linear regression analysis was performed using DUP, gender, age at onset, mode of onset, diagnostic subtype (based on the ICD-9), and premorbid adjustment as independent variables and the outcome assessed with each of the instruments as a dependent variable.

Results

Sample characteristics

Outcome was clarified for 46 (including those who died) of those patients enrolled in the initial study. Of those patients, 34 could be traced and participated in the present interview survey. It was confirmed that 12 patients had died. The causes of death were as follows: suicide, 6; respiratory tract infection, 2; cancer, 2; sudden death, 1; and, kidney failure, 1. The reason all original participants could not be traced was either that they had not sought treatment at any of the medical institutions and thus could not be located or that they did not consent to participate in the survey. DUP was confirmed for 31 of the 34 patients who had been successfully traced and comprised 18 (58.1%) males and 13 (41.9%) females, 16 were outpatients and 15 were inpatients. Mean age was 52.2 years (SD = 8.30; range = 42-72 years). Mean DUP was 8.97 months (SD = 12.99; range = 1-49 months), while median DUP was 3 months. Table 1 shows clinicodemographic data for each of the instruments.

Table 1. Subject characteristics (n = 31)

	Minimum	Maximum	Mean	S.D.
Age (years)	42	72	52.20	8.30
DUP (months)	1	49	8.97	12.99
GAS	11	98	59.16	21.17
DAS comprehensive estimate	0	5	2.19	1.42
CGI	1	7	3.68	1.68

DUP: duration of untreated psychosis
GAS: the Global Assessment Scale
DAS: the Disability Assessment Schedule
CGI: the Clinical Global Impressions

No statistically significant differences were found between the long-DUP and short-DUP groups in relation to the distributions of any of the tested variables, i.e., gender, age at onset, baseline mode of onset, diagnostic subtype (based on the ICD-9), and premorbid adjustment.

None of the tested baseline variables showed a statistically significant difference between the patients who had been traced (n = 31) for this 28-year outcome survey and the patients who had not been traced (n = 66). The untraced patient group showed a tendency to superiority only in relation to premorbid adjustment during childhood (Table 2).

Table 2. Comparison of the traced and untraced subjects in relation to each variable at baseline

Variable	Patients		*P*
	Traced (n = 31)	Untraced (n = 66)	
Male gender, n (%)	18(58.1)	36(54.6)	0.745[a]
Mode of onset, n (%)			0.825[a]
Acute	16(51.6)	34(51.5)	
Insidious	12(38.7)	23(34.9)	
Unknown	3(9.7)	9(13.6)	
Diagnostic subtype, n (%)			0.999[a]
Hebephrenic	16(51.6)	34(51.5)	
Paranoid	9(29.0)	19(28.8)	
Other	6(19.4)	13(19.7)	
Age at onset, (years); mean (SD)	24.0(8.0)	25.1(7.8)	0.403[b]
DUP (months), mean (SD)	8.97(12.99)	10.33(18.84)	
Median	3.0	4.0	0.722[b]
Premorbid adjustment (childhood), n (%)			0.050[a]
Good	21(67.7)	46(69.7)	
Transient conduct or emotional problems	7(22.6)	4(6.1)	
Persistent conduct or emotional problems	1(3.2)	0(0.0)	
Unknown	2(6.5)	16(24.2)	
Premorbid adjustment (adolescence), n(%)			0.142[a]
Good	20(64.5)	41(62.1)	
Transient conduct or emotional problems	8(25.8)	6(9.1)	
Persistent conduct or emotional problems	2(6.5)	1(1.5)	
Unknown	1(3.2)	18(27.3)	

[a]Chi-square test excluding unknown; [b]Wilcoxon rank-sum test
DUP: duration of untreated psychosis

DUP groups

The short DUP group consisted of 16 patients with a DUP of 1.69 ± 0.873 months (mean ± SD) while the long DUP group consisted of 15 patients with a mean DUP of 16.73 ± 15.34 months (mean ± SD). Table 3 compares the short DUP and long DUP groups in regard to outcome with each assessment instrument, showing the mean values (SD). The short DUP group showed a significantly better score than the long DUP group in relation to each of the instruments.

Table 3. Comparison of the outcome in the short DUP and long DUP groups with each instrument

Outcome	Short DUP (n = 16)	Long DUP (n = 15)	*P*
	Mean (S.D.)	Mean (S.D.)	
GAS	73.1(15.2)	44.3(16.0)	<0.001
DAS comprehensive estimate	1.3(0.87)	3.1(1.30)	<0.001
CGI	2.6(1.0)	4.8(1.5)	<0.001

DUP: duration of untreated psychosis
GAS: the Global Assessment Scale
DAS: the Disability Assessment Schedule
CGI: the Clinical Global Impressions

DUP and other factors

The outcome assessed with each of the instruments was subjected to Multiple linear regression analysis as a dependent variable, and a statistically significant association was found between DUP and outcome with each of the assessment instruments even after controlling for various factors other than DUP (i.e., gender, age at onset, mode of onset, diagnostic subtype based on the ICD-9, and premorbid adjustment) (Table 4).

Discussion

This study investigated the relationship between DUP and ultralong-term outcome at 28 years in patients with schizophrenia in Nagasaki, Japan. McGlashan[48] compiled the results of research regarding DUP in first-episode schizophrenia patients in various countries. According to that review, mean DUP was around 1 to 2 years, although there was much variation. The present results support these earlier findings. We found a mean DUP of 8.97 months (SD = 12.99), with a median of 3 months. Yamazawa et al.[15] conducted a prospective study of Japanese first-episode schizophrenia patients at two hospitals in Tokyo between February 2001 and February 2003. They performed a detailed investigation of the association between DUP and outcome after one year. Their results showed a mean DUP of 8.3 months (SD = 13.42), with a median DUP of 3 months. In addition, de Haan et al.[27] investigated the 6-year outcome of schizophrenia patients in Amsterdam, and they reported a mean DUP of 8.6 months (SD = 11.4), with a median DUP of 3 months. These results are very similar to those in the present study.

Table 4. Multiple linear regression analysis: DUP and other factors influencing each instrument

Factor		GAS		DAS comprehensive estimate		CGI	
	Comparison	Regression coefficient	*p*-value	Regression coefficient	*p*-value	Regression coefficient	*p*-value
DUP (months)	≥ 4 vs. ≤ 3	-25.67	0.001	1.58	0.003	2.07	0.002
Age at onset (years)	≥ 25 vs. ≤ 24	5.08	0.496	-0.25	0.633	-0.72	0.258
Gender	Female vs. male	-1.66	0.830	0.58	0.294	0.28	0.663
Mode of onset	Acute vs. insidious or unknown	-1.60	0.797	0.17	0.696	0.09	0.863
Diagnostic subtype							
	Other (reference)	-	-	-	-	-	-
	Hebephrenic	-0.15	0.987	0.41	0.515	0.14	0.846
	Paranoid	8.97	0.361	-0.06	0.936	-0.26	0.750
Premorbid adjustment							
Childhood	Emotional problem vs. good adjustment	5.64	0.472	-0.32	0.558	-0.30	0.649
Adolescence	Emotional problem vs. good adjustment	-1.67	0.840	-0.08	0.888	-0.16	0.812

DUP: duration of untreated psychosis
GAS: the Global Assessment Scale
DAS: the Disability Assessment Schedule
CGI: the Clinical Global Impressions

Looking at the situation in Japan, it is very interesting that very similar characteristics for DUP were elucidated in both our earlier DOSMeD study[37] conducted for 2 years from January 1979 and in the study of Yamazawa et al.[15] covering 2 years from February 2001. The finding that DUP had not shortened despite the long interval of more than 20 years between those two studies can be surmised to indicate that the strategy of early intervention was not well implemented in Japan during that interval. Moreover, it is interesting that the characteristics of DUP were similar in Japan and the Netherlands despite the differences in the two countries' health care systems and racial profiles. In the present study, there were no statistically significant differences in baseline variables between the participants who could be followed up and those who could not. The untraced patient group showed a tendency to superiority only in relation to premorbid adjustment during childhood. These findings confirm that the participants in our study did not represent a special population that deviated from the parent population.

To the best of our knowledge, the present survey represents the first prospective study to minimize biases in the enrollment of subjects and investigate the relationship between DUP and ultralong-term outcome for schizophrenia over more than 25 years from the initial psychiatric consultation. Our results showed a significant association between longer DUP and poorer results for each clinical outcome in terms of psychotic symptoms, degree of social adjustment, and global social functioning. It is often suggested that premorbid adjustment is a confounding factor for the relationship of DUP to outcome[1] in the same manner as other factors, such as gender and age.[4] In our present study, we demonstrated that DUP affects the ultralong-term outcome after a period of 28 years and is independent of such latent confounding factors as gender, age at onset, mode of onset, diagnostic subtype, and premorbid adjustment. We believe this is the first report to document this finding.

There have been many reports of an association between DUP and clinical outcome of schizophrenia. However, most of those studies have investigated the short-term outcome with a follow-up period of only 1 to 2 years.[13-24] There have been some reports of follow-up lasting around 5 years,[25-28] those studies reported an association between DUP and outcome of schizophrenia.

There have been very few reports of studies of the relationship between DUP and long-term outcome of schizophrenia. Of these, some had a long follow-up period of 10 to 20 years and produced similar results to the present study. Bottlender et al.[29] performed a prospective follow-up study of 58 hospitalized schizophrenia patients who were diagnosed according to the DSM-III-R and had no history of psychiatric treatment for similar symptoms. The relationship between the 15-year clinical outcome and DUP was investigated. At the time of data analyses, they took into account the effects of other factors, such as gender, age, premorbid adjustment, and mode of onset. The outcome was significantly worse in the longer DUP patient group on the basis of each of the assessment instruments (the PANSS positive scale, PANSS general psychopathological scale, SANS, and GAS). Wiersma et al.[30] studied a northern Dutch cohort in a WHO collaborative research study that included the DOSMed study and consisted of 63 first-episode schizophrenia patients who had been broadly diagnosed according to the ICD-9. The study investigated the outcome after 15 years. The assessment instruments used included the WHO's DAS and PSE,[49] and the LCS.[50] The results showed that insidious onset and delayed psychiatric treatment were significant predictive factors for greater prolongation of psychotic episodes. Kua et al.[31] studied the outcome of 216 hospitalized schizophrenia patients in Singapore and predictive factors for the outcome over a 20-year follow-up period. The GAS was used as the assessment scale. Logistic regression analysis was performed with adjustment for such factors as gender, race, premorbid character, and age, using clinical outcome as a dependent variable. The analysis found that a shorter "time period from onset of emergency psychotic symptoms until the initial hospitalization" was significantly correlated with a better outcome. Their

study thus demonstrated that, even at 20 years after the first hospitalization, shorter DUP was associated with better outcome.

Summarizing, our findings strongly indicate that DUP is associated with the outcome of schizophrenia, not merely in the short-term, as has been reported by previous studies, but also in the long-term and even the ultralong-term of more than 25 years.

These results support the need to establish a service system that will enable early detection, early intervention, and appropriate early treatment for schizophrenic patients. This is because, in a study that compared a patient group of those whose illness had been detected by the conventional approach and a patient group consisting of those whose illness had been identified by an early detection strategy, it was reported that DUP was shortened as a result of early intervention.[32] Furthermore, Melle et al.[34] investigated DUP for first-episode schizophrenia and the subsequent course in a region to which a comprehensive early-detection system had been introduced and in a region without such a system. Their results showed that DUP was significantly shortened in the region to which the system had been introduced, and confirmed that there was significant alleviation of the negative symptoms, cognitive symptoms, and symptoms of depression after 2 years. These studies indicate that early intervention shortens the DUP, which may lead to improvement of the outcome of schizophrenia. These findings reinforce the importance of establishing and implementing a strategy for early intervention in order to reduce the risk of a poor outcome for schizophrenia even after a long period exceeding 25 years.

We still do not know what neurobiological factors underlie the association between DUP and outcome of schizophrenia. However, the results of a number of studies in relation to DUP and MRI-detected changes in brain structure have been reported. Keshavan et al.[51] investigated brain structural changes one year after commencing therapy in first-episode schizophrenia patients who had been neuroleptic-naive. They found that DUP showed a negative correlation with the volume of the left superior temporal gyrus. In addition, Lappin et al.[52] investigated the relationship between DUP and brain structural changes to determine whether a brain anatomical abnormality was the cause of a poor outcome of psychosis. They reported that the longer the DUP, the more striking the reduction in the volume of the left temporal lobe gray matter. In recent years, Brain-derived neurotrophic factor (BDNF) has been suggested to be involved in the etiology of schizophrenia. For example, a significant reduction in BDNF mRNA and protein was found in the prefrontal cortex of patients with schizophrenia in postmortem studies.[53] A deficit in this neurotrophic factor may contribute to the structural alterations of brain underlying in the psychopathology of schizophrenia. These findings may help in elucidating the mechanism underlying the association between DUP and the outcome of schizophrenia. However, it is clear that much further research is required.

The present study has its own merits and limitations. Merits include the unusually long follow-up period and the fact that participants reflected a homogeneous aggregate of the disease. Establishment of the CFN made it possible to recruit a uniform population as criteria were sufficiently precise to enable calculation of the incidence and annual prevalence of schizophrenia.[30,37] Application of this method made it possible to eliminate any bias that might arise from the medical institution at which a patient was being treated. Moreover, patients were not classified as inpatients and outpatients and were all first-episode cases of schizophrenia. Therefore, the study population was highly suited for analysis of the essence of schizophrenia. For that reason, we think that our present study accurately and faithfully reflects the outcome of this disease. A third merit of our study is that, as reported by Marshall et al.,[1] the information regarding DUP was accurately evaluated at the time of first contact. This is the first published investigation of the association between DUP and the outcome of schizophrenia over an ultra-long study period of 28 years.

With regard to the limitations of this study, it is clear that the number of participants was relatively small, while the dropout rate was high. Nearly 60% of the original participants could not be traced, for the following possible reasons. First, in the DOSMeD study that served as the basis of the present study, approximately 40% of the participants became untraceable within the first 1-2 years of the study.[36] In addition, although the earlier surveys were conducted after 1, 2, 5, 10, and 15 years, i.e., no interval was longer than 5 years, the survey performed after 28 years had a long interlude of 13 years following the previous survey. Moreover, in the DOSMeD study, the participants were not restricted to hospitalized patients or patients being treated at designated hospitals, but were instead recruited from multiple institutions. For that reason, the participants consisted of schizophrenia patients who were recruited within a certain geographical area. This made it difficult to establish the addresses of the participants. The present study is the first to recruit subjects at a large number of medical institutions and to investigate DUP over such a long period. Kua et al.[31] performed a study with a 20-year follow-up period while Bottlender et al.[29] conducted a 15-year outcome study, and follow-up may have been easier in those studies because they both enrolled inpatients. Even so, Kua et al.[31] reported a dropout rate of 30% over the 20-year period. Taken together, we conclude that the high dropout rate in our present study was a natural phenomenon and unavoidable. Although the dropout rate was high, analysis of the demographic variables found no significant differences between the traced and untraced subjects. Accordingly, any effects on the validity and generalizability of the results are likely to be minimal. However, it is possible that the patient group with a good outcome includes some patients who did not need to consult a medical institution. There are ethical concerns with making contact with such patients showing a good outcome. For that reason, it is possible that the patient group with a good outcome underwent small sampling.

Acknowledgments

The present research was supported by Basic Scientific Research

Grant (C) No. 18591294 from the Japanese Ministry of Health, Labour and Welfare.

The authors express their sincere gratitude to all staff of the CFN and to all participants and their families for their cooperation in this study. We are also deeply indebted to all of the psychiatrists belonging to the Social Psychiatry Research Group of the Department of Neuropsychiatry of Nagasaki University Graduate School of Biomedical Sciences and who participated in the DOSMeD Study.

References

1. Marshall M, Lewis S, Lockwood A, Drake R, Jones P, Croudace T.: Association between duration of untreated psychosis and outcome in cohorts of first-episode patients: a systematic review. *Arch Gen Psychiatry* Sep 62(9): 975-983, 2005
2. Loebel AD, Lieberman JA, Alvir JM, et al. Duration of psychosis and outcome in first-episode schizophrenia. *Am J Psychiatry* 149: 1183-1188, 1992
3. Perkins DO. Review: Longer duration of untreated psychosis is associated with worse outcome in people with first episode psychosis. *Evid Based Ment Health* 9(2): 36, 2006
4. Perkins DO, Gu H, Boteva K, Lieberman JA.: Relationship between duration of untreated psychosis and outcome in first-episode schizophrenia: a critical review and meta-analysis. *Am J Psychiatry* 162(10): 1785-1804, 2005
5. Farooq S, Large M, Nielssen O, Waheed W. The relationship between the duration of untreated psychosis and outcome in low-and-middle income countries : A systematic review and meta analysis. *Shizophr Res* 109; 15-23, 2009
6. Larsen TK, McGlashan TH, Moe LC. First-episode schizophrenia: I. Early course parameters. *Shizophr Bull* 22(2): 241-256, 1996
7. Harrigan SM, McGorry PD, Krstev H. Does treatment delay in first-episode psychosis really matter? *Psychol Med* 33(1):97-110.2003
8. Drake RJ, Haley CJ, Akhtar S, Lewis SW. Causes and consequences of duration of untreated psychosis in schizophrenia. *Br J Psychiatry* 177: 511-515, 2000
9. Black K, Peters L, Rui Q, Milliken H, Whitehorn D, Kopala LC. Duration of untreated psychosis predicts treatment outcome in an early psychosis program. *Schizophr Res* 47: 215-222, 2001
10. Szymanski SR, Cannon TD, Gallacher F, Erwin RJ, Gur RE. Course of treatment response in first-episode and chronic schizophrenia. *Am J Psychiatry* 153: 519-525, 1996
11. Uçok A, Polat A, Genc A , Turan N.. Duration of untreated psychosis may predict acute treatment response in first-episode schizophrenia. *J Psychiatr Res* 38: 163-168, 2004
12. Wunderink A, Nienhuis FJ, Sytema S, Wiersma D. Treatment delay and response rate in first episode psychosis. *Acta Psychiatr Scand* 113(4): 332-9, 2006.
13. Fuchs J, Steinert T. Dauer der unbehandelten psychose (DUP) : ein brauchbarer pradiktor fur den krankheitsverlauf? [Duration of untreated psychosis (DUP) :An useful predictor of outcome in schizophrenia?] *Fortschr Neurol Psychiatr* 72: 79-87, 2004
14. Yamazawa R, Mizuno M, Nemoto T, Miura Y, Murakami M, Kashima H. Duration of untreated psychosis and pathways to psychiatric services in first-episode schizophrenia. *Psychiatry Clin Neurosci* 58: 76-81, 2004
15. Yamazawa R, Nemoto T, Kobayashi H, Chino B, Kashima H, Mizuno M. Association between duration of untreated psychosis, premorbid functioning, and cognitive performance and the outcome of first-episode schizophrenia in Japanese patients: prospective study. *Aust N Z J Psychiatry* 42: 159-165, 2008
16. Ucok A, Polat A, Cakir S, Genc A. One year outcome in first episode schizophrenia. Predictors of relapse. *Eur Arch Psychiatry Clin Neurosci* 256(1): 37-43, Epub 2005 Jul 18.2006
17. Larsen TK, Moe LC, Vibe-Hansen L, Johannessen JO. Premorbid functioning versus duration of untreated psychosis in 1 year outcome in first-episode psychosis. *Shizophr Res* 45: 1-9, 2000
18. Malla AK, Norman RM, Manchanda R, et al. One year outcome in first episode psychosis: influence of DUP and other predictors. *Schizophr Res* 54: 231-242, 2002
19. Barnes T RE, Leeson VC, Mutsatsa SH, Watt HC, Hutton SB, Joyce EM. Duration of untreated psychosis and social function: 1-year follow-up study of first-episode schizophrenia. *Br J Psychiatry* 193: 203-209, 2008
20. Perkins DO, Lieberman JA, Gu H,et al. Predictors of antipsychotic treatment response in patients with first-episode schizophrenia, schizoaffective and schizophreniform disorders. *Br J Psychiatry* 185: 18-24, 2004
21. Oosthuizen P, Emsley RA, Keyter N, Niehaus DJ, Koen L. Duration of untreated psychosis and outcome in first-episode psychosis. Perspective from a developing country. *Acta Psychiatr Scand* 111(3): 214-9, 2005
22. Schimmelmann BG, Huber CG, Lambert M, Cotton S, McGorry PD, Conus P. Impact of duration of untreated psychosis on pre-treatment, baseline, and outcome characteristics in an epidemiological first-episode psychosis cohort. *J Psychiatr Res* 42: 982-990, 2008
23. Addington J, Vanmastrigt S, Addington D. Duration of untreated psychosis: impact on 2-year outcome. *Psychol Med* 34: 277-284, 2004
24. Keshavan MS, Haas G, Miewald J,et al. Prolonged untreated illness duration from prodromal onset predicts outcome in first episode psychoses. *Schizophr Bull* 29(4): 757-769, 2003
25. Clarke M, Whitty P, Browne S, et al. Untreated illness and outcome of psychosis. *Br J Psychiatry* 189: 235-240, 2006
26. Altamura AC, Bassetti R, Sassella F, Salvadori D, Mundo E. Duration of untreated psychosis as a predictor of outcome in first-episode schizophrenia: a retrospective study. *Schizophr Res* 52: 29-36, 2001
27. de Haan L, Linszen DH, Lenior ME, de Win ED, Gorsira R. Duration of untreated psychosis and outcome of schizophrenia: delay in intensive psychosocial treatment versus delay in treatment with antipsychotic medication. *Schizophr Bull* 29(2): 341-8, 2003
28. Harris MG, Henry LP, Harrigan SM, et al. The relationship between duration of untreated psychosis and outcome: An eight-year prospective study. *Schizophr Res* 79: 85-93, 2005
29. Bottlender R, Sato T, Jäger M, et al. The impact of the duration of untreated psychosis prior to first psychiatric admission on the 15-year outcome in schizophrenia. *Schizophr Res* 62: 37-44, 2003
30. Wiersma D, Nienhuis FJ, Slooff CJ, Giel R. Natural course of schizophrenic disorders: a 15-year followup of a Dutch incidence cohort. *Schizophr Bull* 24(1): 75-85, 1998
31. Kua J, Wong KE, Kua EH, Tsoi WF. A 20-year follow-up study on schizophrenia in Singapore. *Acta Psychiatr Scand* 108: 118-125, 2003
32. Larsen TK, McGlashan TH, Johannessen JO, et al. Shortened duration of untreated first episode of psychosis: changes in patient characteristics at treatment. *Am J Psychiatry* 158(11): 1917-9, 2001
33. Melle I, Larsen TK, Haahr U,et al. Reducing the duration of untreated first-episode psychosis. Effects on clinical presentation. *Arch Gen Psychiatry* 61: 143-150, 2004
34. Melle I, Larsen TK, Haahr U, et al.. Prevention of negative symptom psychopathologies in first-episode schizophrenia: Two-year effects of reducing the duration of untreated psychosis. *Arch Gen Psychiatry* 65(6): 634-640, 2008
35. Novak Sarotar B, Pesek MB, Agius M, Kocmur M. Duration of untreated psychosis and it's effect on the symptomatic recovery in schizophrenia - preliminary results. *Neuro Endocrinol Lett*. 29(6): 990-4. 2008
36. Nakane Y, Takada K, Yoshitake K, Hatada K. DOSMeD: Nagasaki, Japan. In *Recovery from Schizophrenia: an international perspective. A report from the WHO collaborative project, the international study of schizophrenia* (Hopper K, Harrison G, Janca A, Sartorius N eds.; Oxford University Press, Oxford) pp. 164-176, 2007
37. Nakane Y, Ohta Y & Radford MHB. Epidemiological Studies of schizophrenia in Japan. *Schizophrenia Bulletin* 18(1): 75-84, 1992
38. Jablensky A, Sartorius N, Ernberg G et al. *Schizophrenia: Manifestations, Incidence and Course in Different Cultures: A World Health Organization Ten-country Study. Psychological Medicine Monograph, Suppl 20*, Cambridge University Press, Cambridge, 1992
39. Kramer M, Sartorius N, Jablensky A, Gulbinat W. The ICD-9 classification of mental disorders : a review of its development and contents. *Acta Psychiatr Scand* 59: 241-262, 1979
40. The ICD-10 Classification of Mental and Behavioral Disorders: Clinical descriptions and diagnostic guidelines. *World Health Organization*, Geneva, 1992
41. Takada K, Yoshitake K, Nakane Y, et al. Nagasaki Schizophrenia Study: Outcome of a 15-year follow-up of an incident cohort. *Acta Med Nagasaki* 42: 39-44, 1997
42. Kinoshita H, Nakane Y, Nakane H, et al. Nagasaki Schizophrenia Study: Influence of the duration of untreated psychosis on long-term outcome. *Acta Med Nagasaki* 50: 17-22, 2005
43. WHO Psychiatric Disability Assessment Schedule (WHO/DAS), *World Health Organization*, Geneva, 1988
44. Endicott J, Spitzer RL, Fleiss JL, Cohen J. The Global Assessment Scale. A pro cedure for measuring overall severity of psychiatric disturbance. *Arch Gen Psychiatry* 33: 766-771, 1976
45. Leon AC, Shear MK, Klerman GL. A comparison of symptom determinants of patient and clinician global ratings in patients with panic disorder and depression. *J Clin Psychopharmacol* 13(5): 327-331, 1993

46. Cannon-Spoor HE, Potkin SG, Wyatt RJ. Measurement of premorbid adjustment in chronic schizophrenia. *Shizophr Bull* 8(3): 470-484, 1982
47. Gupta S, Rajaprabhakaran R, Arndt S, Flaum M, Andreasen NC. Premorbid adjustment as a predictor of phenomenological and neurobiological indices in schizophrenia. *Schizophr Res* 16(3): 189-97, 1995
48. McGlashan TH. Duration of untreated psychosis in first-episode schizophrenia: Marker or determinant of course? *Biol Psychiatry* 46: 899-907, 1999
49. Wing, J.K.; Cooper, J.E.; and Sartorius, N. *The Measurement and Classification of Psychiatric Symptoms.* England: Cambridge University Press, Cambridge, 1974
50. WHO Life Chart Schedule (LCS), *World Health Organization*, Geneva, 1992
51. Keshavan MS, Haas GL, Kahn CE, et al. Superior temporal gyrus and the course of early schizophrenia: progressive, static, or reversible? *J Psychiatr Res* 32(3-4): 161-167, 1998
52. Lappin JM, Morgan K, Morgan C, et al Gray matter abnormalities associated with duration of untreated psychosis. *Schizophr Res* 83: 145-153, 2006
53. Weickert CS, Hyde TM, Lipska BK, Herman MM, Weinberger DR, Kleinman JE. Reduced brain-derived neurotrophic factor in prefrontal cortex of patients with schizophrenia. *Mol Psychiatry* 8(6): 592-610, 2003