Nagasaki Schizophrenia Study: Influence of the Duration of Untreated Psychosis on Long-Term Outcome

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To elucidate the association between the duration of untreated psychosis and long-term outcome in schizophrenic patients, we followed up a cohort of first-episode schizophrenic patients in Nagasaki. The present study was conducted in the framework of the World Health Organization Collaborative Study on Determinants of Severe Mental Disorders, which our research group participated in as The Nagasaki World Health Organization Collaborating Center for Research and Training in Mental Health. The cohort was established during the period from 1979 to 1980 and consisted of 107 patients initially diagnosed as schizophrenia according to ICD-9. The subjects of the present study were 97 members of the cohort (54 males and 43 females) in whom we could measure the duration of untreated psychosis. The 97 study subjects were followed up for 15 years since they were enrolled in the cohort and were checked their mental conditions at 1-, 2-, 5-, 10- and 15-year follow-up points. The triplet of the 1st, 2nd and 3rd quartiles of the duration of untreated psychosis in them was (1, 4, 12) months (the mean was 9.9 months). During the whole period of 15-year follow-up, 5 patients died, 40 were lost for follow-up and 52 remained contacted at 15-year follow-up point; out of these 52 patients, 22 were contacted through the whole period. During the first 10 years of the follow-up, the patients diagnosed to have completely been remitted at follow-up point showed a significantly or marginally shorter duration of untreated psychosis as compared to those diagnosed not to have completely remitted; the triplet of the 1st, 2nd and 3rd quartiles of the duration of untreated psychosis in those diagnosed to have completely remitted at 1-year follow-up point was (1, 3, 4) months, while that in those diagnosed not to have completely remitted at the same follow-up point was (2, 6, 12) months and the difference was significant (p=0.036, Wilcoxon rank-sum test). Similarly, the triplets of the 1st, 2nd and 3rd quartiles of the duration of untreated psychosis in the two groups diagnosed with and without complete remission at 2-, 5- and 10-year follow-up points were (1, 3, 4) and (2, 6, 17) months (p=0.021), (1, 3, 8) and (1, 6, 17) months (p=0.149), and (1, 2, 3) and (3, 6, 12) months (p=0.008), respectively. However, no difference was observed between the two groups at 15-year follow-up point; (1, 4, 12) and (1, 4, 9) months (p=0.828). The results of the present study indicate that the duration of untreated psychosis will probably influence on the outcome of schizophrenia at least 10 years.

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Introduction

Many studies on first-episode schizophrenic patients have shown that the duration of untreated psychosis (DUP) and psychiatric admission often last months or years. There is evidence that schizophrenic patients with a longer DUP show poorer response to acute treatment, thus resulting in worse short-term outcome, compared to those with a shorter DUP.[1-5] However, only a few studies have dealt with the possible association between DUP and long-term outcome.[6-9] Moreover, most of previous studies were retrospective and/or used less restrictive concepts for schizophrenia than the diagnostic criteria in ICD-9/10, thus limiting their conclusions.

Compared to other countries, patients in Japan have longer hospital stays. Other characteristics of the Japanese system are a large

number of psychiatric beds per unit of population, of which more than 90% are in private hospitals, and the strong stigma associated with mental disorders. In Japan, there have been a few reports on the relationship between DUP and outcome of schizophrenia patient.[10,11] The present paper reports the relationship between DUP and long-term outcome of first-episode schizophrenic patients in Japan.

The patients included in this study were recruited in a clearly-defined catchment area. The patients were diagnosed with schizophrenia according to the ICD-9 criteria and were followed from first contact to 1, 2, 5, 10, and 15 years later.

Methods and Subjects

Background

The present study was based on the World Health Organization (WHO) Collaborative Study on Determinants of Severe Mental Disorders (DOSMeD Study), which our research group participated in as The Nagasaki World Health Organization Collaborating Center for Research and Training in Mental Health.[12,13] The DOSMeD study was commenced in 1979 and is still continuing. WHO gave the DOSMeD Study the status of the second stage of the International Pilot Study of Schizophrenia (IPSS).[14] The IPSS, which was commenced in 1965, established the basic epidemiological research methodology on the study of mental disease. In addition, it elucidated the clinical and psychosocial character of schizophrenia and cleared up differences in outcomes of schizophrenia in participating countries. The main goals of the DOSMeD Study were to confirm the IPSS data and to calculate the incidence rates of schizophrenia in participating countries.

Subjects

Prior to the DOSMeD Study, we conducted a preliminary study under the protocol of the DOSMeD Study in October and November 1978 to determine the pattern that patients residing in Nagasaki city consult doctors for mental disorders.[12] We confirmed from the preliminary study that patients residing in Nagasaki city would probably be found completely if we could obtain the cooperation of the following 30 psychiatric care organizations in Nagasaki city and its vicinity: 18 private mental hospitals, 1 mental hospital of Nagasaki prefecture, 5 private psychiatric clinics, 4 psychiatry departments of public general hospitals and 2 health care centers.

Medical doctors at the Department of Nueropsychiatry of Nagasaki University Hospital (called researchers for short) called the 30 cooperating facilities by telephone at around 11 a.m. every day for 2 years, from January 1, 1979 to December 31, 1980, and asked about new cases that could be included in this study. Table 1 shows the adoption criteria for this study. Patients who had an organic brain disorder or who were dependent on alcohol or drugs were excluded. A researcher visited the facility, which made a positive response, to explain the patient and family the purpose and methods of this study, and if they agreed to participate in this study, the structured

Table 1. Adoption criteria for the World Health Organization Collaborative Study on Determinants of Severe Mental Disorders (DOSMeD Study)[13]

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

(a) During the past one year the patient had at least one of the following.

   1. Hallucinations or pseudo hallucinations in any mordality

   2. Delusions

   3. Marked thought and speech disorder (e.g., incoherence, irrelevance, thought blocking, neologisms, and 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, etc.)

(b) During the past one year, patients had presented a definite change of personality and behavior for at least one of the following.

   1. Marked reduction or loss of interest, initiative and drive, leading to serious deterioration of the 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

interviews were conducted for patients by using the assessment schedules. After the consultation period, we conducted a leakage study to find cases not then reported from the facilities. We also enrolled patients who did not meet the adoption criteria at first contact but did so later. The procedure used for selecting new schizophrenic patients, reported in detail elsewhere,[12] was epidemiologically accurate enough for evaluating the incidence rate of schizophrenia in Nagasaki city.

The DOSMeD Study in Nagasaki enrolled a total of 107 patients who were initially diagnosed as schizophrenia according to ICD-9. The subjects of the present study were 97 members of the Nagasaki DOSMeD Study cohort in whom we could measure the duration of untreated psychosis (DUP).

Study instruments

Table 2 shows the instruments that were used at the commencement of the DOSMeD Study. All interviews were done by psychiatrists who had been trained in the use of these instruments. In this study we measured DUP from the Psychiatric and Personal History Schedule (PPHS, WHO 1978)[13] in Table 2. The PPHS contains over 200 items for assessment, such as personal history, history of present illness and family illness, as well as social and economic factors. The PPHS also determines the time of onset of schizophrenia, judged by the researcher who interviewed the patient. We defined the DUP as the period in months between the onset of the illness and the time of initial visit at a medical facility.

Table 2. Instruments used in the World Health Organization Collaborative Study on Determinants of Severe Mental Disorders (DOSMeD Study) at first assessment

Instruments	Contents
PPHS: Psychiatric and Personal History Schedule (WHO, 1978)[13]	Family history, life history, etc.
DPS: Diagnostic and Prognostic Schedule (WHO, 1978)[13]	Previous illness, present illness, diagnosis, outcome, etc.
PSE-9: Present State Examination 9th edition (Wing et al., 1974)[15]	Psychotic symptoms in the last month
LES: Life Event Schedule (WHO, 1978)[13]	Life events, etc.
KAS: Katz Adjustment Schedule (Katz et al., 1963)[16]	Adjustments for home and society

Definition and classification of outcomes

In this study, remission was defined as no symptoms or signs of a psychotic episode for at least 4 weeks. Complete remission was defined as the state of no symptoms and maintenance of the natural character that existed before the illness. Incomplete remission was defined as not being psychotic but having (1) residual symptoms, (2) non-psychotic symptoms or (3) a character change. We then classified the courses of disease into 5 categories shown in Figure 1 according to the PPHS: complete remission with no relapse, complete remission with relapse, incomplete remission with no relapse, incomplete remission with relapse and continuous psychotic illness; we called the group of the first two categories " good outcome" and the other group of the remaining categories " poor outcome."
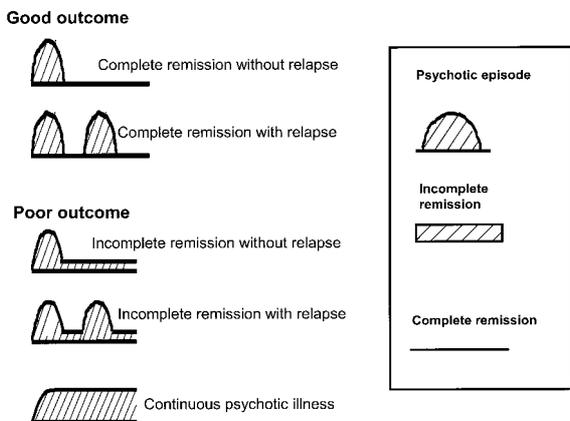

Figure 1. Classification of the course of illness. We call the group of the first two categories, i.e., complete remission without relapse and complete remission without relapse, " good outcome" and the other group of the remaining categories " poor outcome."

Statistical analysis

We used the items for the course of the disease in the PPHS to assess the outcome of the disease at 1-, 2-, 5- and 10-year follow-up points; in 1984-1985 and 1990-1991, Nagasaki University carried out 5- and 10-year follow-up studies on the course and the outcome for the present subjects. The outcome of the disease at 15-year follow-up point was assessed using the schedule of the WHO International Study of Schizophrenia (ISoS), which was initiated by WHO in 1994-1995 as the 15-year follow-up of the DOSMeD.[17,18]

We analyzed the relationship between DUP and the outcome of the disease at 1-, 2-, 5-, 10- and 15-year follow-up points by comparing the distribution of DUP between the two groups of the patients with and without complete remission at respective follow-up points; we used Wilcoxon rank-sum test for comparison. PROC NPAR1WAY and PROC UNIVARIATE of SAS system were used for the necessary calculation.

Results

Out of 97 patients in the present study, 54 (55.7%) were males and 43 (44.3%) were females. The age at onset of the disease varied from 15 to 53 years, and the triplet of the 1st, 2nd and 3rd quartiles was (19, 23, 29) years with the mean (standard deviation) of 24.8 (7.82) years. Eight (8.2%) patients were living alone and 89 (91.8%) were living with their families. Seventy-five (77.3%) were single, 18 (18.6%) were married and 4 (4.1%) were divorced.

The duration of untreated psychosis (DUP) of patients varied from 1 to 132 months and the triplet of the 1st, 2nd and 3rd quartiles was (1, 4, 12) months with the mean (standard deviation) of 9.9 (17.1) months. The DUP did not differ significantly between males and females ($p=0.443$) as shown in Figure 2.
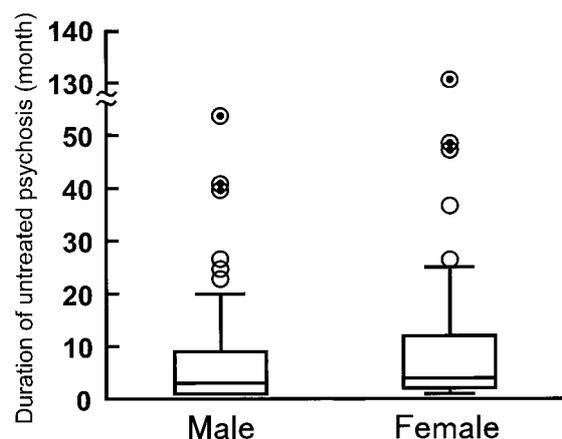

Figure 2. Box-and-whisker plots of the duration of untreated psychosis (month) by gender. The bottom and top ends of the box and the bar inside the box correspond to the 1st, 3rd and 2nd quartiles of the sample (or 25th, 75th and 50th sample percentiles), respectively. The open circle and the double circle with black dot represent extreme values called " outside" and " far out," respectively.

The behavior of patients in participation in the study was very complicated as shown in Figure 3. The proportion of participating patients decreased steadily at 1-, 2- and 5-year follow-up points (75.3%, 67.0% and 51.5%, respectively) then remained stable at 10- and 15-year follow-up points (53.6% and 53.6%, respectively).
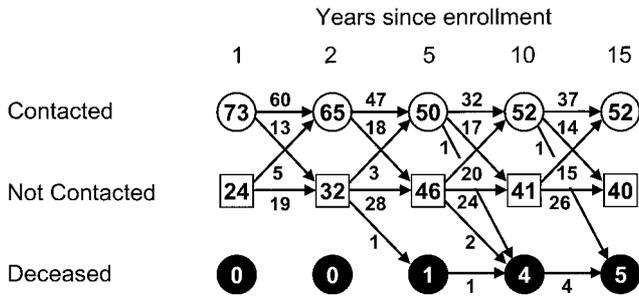

Figure 3. Dynamics of patients' participation in the study through the follow-up. The numerals in the open circle, box and closed circle denote the number of patients who were contacted, not contacted and deceased at respective follow-up points. The numerals on the line connecting two nodes (open circle, box or closed circle) denote the number of patients who moved from one node to the other node.

The outcomes of patients contacted at respective follow-up points showed a complicated pattern as well (Figure 4). The proportion of patients with complete remission gradually decreased while that of those with incomplete remission or with continuous psychotic illness gradually increased; however, the change was not large except for the first two years. The breakdown of patients shown in Figure 4 at respective follow-up points was as follows: the number of patients with complete remission without relapse (with relapse in parentheses) was 15 (16), 6 (20), 6 (11), 3 (14) and 4 (13) at 1-, 2-, 5-, 10- and 15-year follow-up points, respectively; the number of patients with incomplete remission without relapse (with relapse in parentheses) was 14 (2), 14 (5), 9 (18), 3 (22) and 0 (17) at 1-, 2-, 5-, 10- and 15-year follow-up points, respectively; and the number of patients with continuous psychotic illness was 26, 20, 6, 10 and 18 at 1-, 2-, 5-, 10- and 15-year follow-up points, respectively.
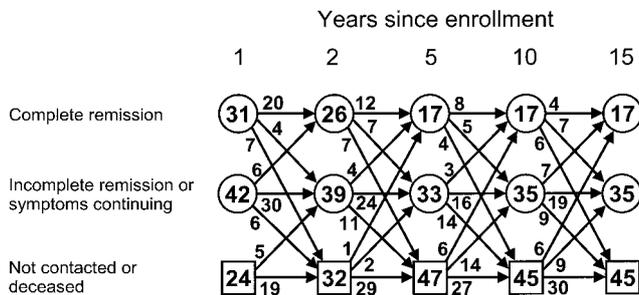

Figure 4. Dynamics of the outcomes in the patients through the follow-up. The numerals in the open circle, box and closed circle denote the number of patients who were contacted, not contacted and deceased at respective times of the follow-up. The numerals on the line connecting two nodes (open circle, box or closed circle) denote the number of patients who moved from one node to another node.

Figure 5 compares the distribution of DUP in patients with complete remission (good outcome group) and that in those with incomplete remission or with continuous psychotic illness (poor outcome group) classified by the outcome observed at respective follow-up points. During the first 10 years of the follow-up, the patients with good outcome at each follow-up point showed a significantly or marginally shorter DUP as compared to those with poor outcome; the triplet of the 1st, 2nd and 3rd quartiles of the DUP in those with good outcome at 1-year follow-up point was (1, 3, 4) months, while that in those with poor outcome at 1-year follow-up point was (2, 6, 12) months and the difference was significant (p =0.036). Similarly, the triplets of the 1st, 2nd and 3rd quartiles of the DUP in the two groups with good and poor outcomes at 2-, 5- and 10-year follow-up points were (1, 3, 4) and (2, 6, 17) months (p=0.021); (1, 3, 8) and (1, 6, 17) months (p=0.149); and (1, 2, 3) and (3, 6, 12) months (p=0.008). However, no difference was observed between the two groups at 15-year follow-up point; (1, 4, 12) and (1, 4, 9) months (p=0.828).
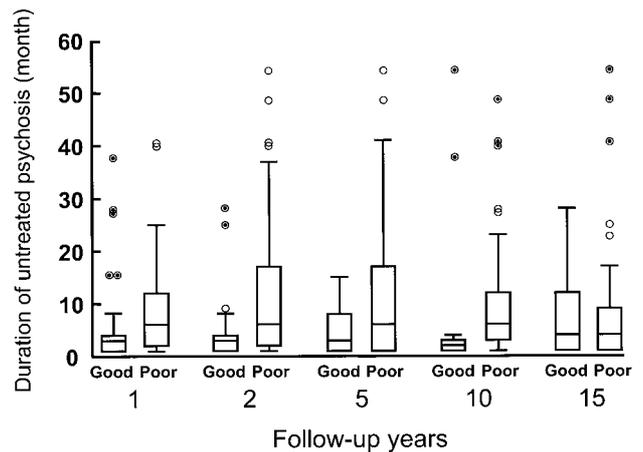

Figure 5. Box-and-whisker plots of the duration of untreated psychosis (month) by outcome at the time of the follow-up. Good: complete remission without relapse or complete remission with relapse; Poor: incomplete remission without relapse, incomplete remission with relapse or symptoms continuing. See Figure 2 for the details of the plots.

Discussion

The duration of untreated psychosis in the patients of the present study varied from 1 to 132 months with the median of 4 months and is compatible with that reported by other studies[3,4,10,11,19-23] (Table 3).

Norman and Malla[24] stated in their review of DUP," On balance, it seemed fair to say that there was evidence suggesting a relationship between DUP and the initial response to treatment, although the robustness of such findings and their independence from all potential confounding variables yet to be established." In another follow-up study, Malla et al.[23] examined the relationship between DUP and several other predictors and 1-year outcome, and they confirmed the independent role of DUP in remission and positive symptoms at 1-year follow-up point, thus providing support for

Table 3. The duration of untreated psychosis reported by other studies and the present study[13]

Study	Number of patients	Median (month)	Mean (month)
Lobel et al. (1992)[4]	70	9.75	13.0
Beiser et al. (1993)[19]	72	2	14
Larsen et al. (1996)[20]	43	6.5	28.5
McGrorry et al. (1996)[3]	200	7.5	56.3
Browne et al. (2000)[21]	53	6.5	22.7
Thomas et al. (2000)[22]	52	6.5	14.8
Malla et al. (2002)[23]	88	—	11.2
Kobayashi (2002)[10]	62	1	8.7
Yamazawa et al. (2004)[11]	83	—	13.7
Present study	97	4	9.9

[a]The duration of untreated psychosis was measured in week in the first 7 studies and we converted those measurements in month by equating 4 weeks with 1 month.

Table 4. Status of patients at each follow-up point by duration of untreated psychosis

Follow-up point	Status[a]	Duration of untreated psychosis (month)[b]			
		1–3 (48)	4–6 (16)	7–12 (13)	13– (20)
1-year	Good	20 (41.7)[c]	5 (31.3)	1 (7.7)	5 (25.0)
	Poor	17 (35.4)	7 (43.8)	9 (69.2)	9 (45.0)
	Missing	11 (22.9)	4 (25.0)	3 (23.1)	6 (30.0)
2-year	Good	16 (33.3)	6 (37.5)	2 (15.4)	2 (10.0)
	Poor	16 (33.3)	4 (25.0)	8 (61.5)	11 (55.0)
	Missing	16 (33.3)	6 (37.5)	3 (23.1)	7 (35.0)
5-year	Good	10 (20.8)	2 (12.5)	3 (23.1)	2 (10.0)
	Poor	13 (27.1)	6 (37.5)	4 (30.8)	10 (50.0)
	Missing	25 (52.1)	8 (50.0)	6 (46.2)	8 (40.0)
10-year	Good	13 (27.1)	2 (12.5)	0 (0.0)	2 (10.0)
	Poor	11 (22.9)	9 (56.3)	7 (53.8)	8 (40.0)
	Missing	24 (50.0)	5 (31.3)	6 (46.2)	10 (50.0)
15-year	Good	8 (16.7)	3 (18.8)	2 (15.4)	4 (20.0)
	Poor	15 (31.3)	7 (43.8)	7 (53.8)	6 (30.0)
	Missing	25 (52.1)	6 (37.5)	4 (30.8)	10 (50.0)

[a]Good: complete remission without relapse or complete remission with relapse;

Poor: incomplete remission without relapse, incomplete remission with relapse or symptoms continuing;

Missing: not contacted or deceased.

[b]Number of patients in parentheses.

[c]Number of patients (percentage).

early intervention. In the present study, a longer DUP was significantly associated with a poor outcome at 1- and 2-year follow-up points. This result was in line with other prospective studies. These results suggested that DUP could be used as a predictor of the short-term outcome of schizophrenia. Malla et al.[23] also suggested the importance of early detection and intervention for schizophrenia.

Regarding the long-term outcome, Norman and Malla[24] reported that there have been few investigations of the relationship of DUP to long-term outcomes, such as negative symptoms and cognitive functioning; nor were possible confounders of DUP investigated widely. However, the findings of Bottlender et al.,[25] who later investigated DUP and the outcomes of 58 patients at 15-year follow-up point, combined with those reported by previous studies, strongly suggested that the DUP was not only associated with short-term but also long-term outcome in schizophrenia.

In the present study, the DUP was lower in patients with good outcome than in those with poor outcome within 10 years from the commencement of follow-up; the difference was significant at 1-, 2- and 10-year follow-up points ($p=0.036$, $p=0.021$ and $p=0.008$, respectively) but it was not significant at 5-year follow-up point ($p=0.149$). The insignificant difference in the DUP between the two groups at 5-year follow-up point was mainly due to the fact that a significant proportion of patients with good outcome and relatively short DUP at 2-year follow-up point were not contacted at 5-year follow-up point (Table 4). These results suggest that the DUP could be used as a predictor of the outcome of schizophrenia at least up to 10 years. In contrast to the study by Bottlender et al.,[25] the present study showed no difference in DUP between the patients with good and poor outcomes at 15-year follow-up point.

Although we followed up the cohort of schizophrenic patients, main analysis in the present study was of the repetition of cross-sectional analyses. The reason we used such analysis was: (1) the patients' behavior in participation was very complicated in that some patients not contacted at one follow-up point were contacted at another follow-up point and vice versa; (2) no information was

available for patients' mental condition at the time of not contacted; (3) the outcome alternated in some patients between good one and poor one through the follow-up. Although we could not perform formal analysis, which should be most appropriate, we tried to examine the temporal changes in the outcome of the cohort members by DUP (Table 4).

The results (including Table 4) of the present study suggest that the DUP could probably influence the course of illness in schizophrenic patients for about 10 years at most, and thereafter the influence of other factors such as medication and other treatments, social support, support from the family and life style may be greater.

The present study ultimately underscores the importance of early detection of first-episode schizophrenic patients and early intervention in them; early detection is inevitable for immediate reduction in unnecessary suffering and early intervention will increase the likelihood to improve the long-term outcome. Early detection and intervention programs represent an extremely important innovation in the treatment of schizophrenia. Unfortunately, we were unable to carry out a 20-year follow-up, but we are now preparing to perform a 25-year follow-up on these patients.

Acknowledgments

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