

Nagasaki Schizophrenia Study : Outcome of a 15-year Follow-up of an Incident Cohort

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The Nagasaki World Health Organization (WHO) Collaborating Center for Research and Training in Mental Health conducted the WHO Coordinated Multi-Center Study of the Long-term Course and Outcome of Schizophrenia as a part of the International Study on Schizophrenia (ISoS). The study used 107 patients who were initially diagnosed as having ICD-9 schizophrenia for the WHO Collaborative Study on the Determinants of Outcome of Severe Mental Disorders (DOSMeD). Subjects were first collected in 1979-1980 for an incidence study of schizophrenia in Nagasaki. In this 15-year follow-up study, 7 subjects died, 43 subjects were lost to follow-up and 57 were successfully traced. Among the 7 death cases, 4 suicides were confirmed and 1 was suspected. During the 15-year period, 25 (44%) of the 57 living subjects displayed continuous psychotic course type schizophrenia. During the last 2 years, 14 (25%) were not psychotic; 31 (54%) were continuously psychotic. Global Assessment of Functioning Scale for Symptomatology (GAF-S) indicated symptomatological outcomes: 16 (28%) had severe symptoms (GAF-S < 51), and 17 (30%) were symptom-free (GAF-S > 70). Social outcome was evaluated using the Global Assessment of Functioning Scale for Disability (GAF-D): 28 (49%) showed poor adjustment (GAF-D < 51), and 23 (40%) were functioning well (GAF-D > 70). The overall time trend was almost evenly divided in thirds: 20 (35%) were getting better, 18 (32%) were the same and 19 (33%) were worse. The present study showed that the outcome of schizophrenia is not always poor, although some patients display a continuous course and poor outcome.

Key Words : schizophrenia, outcome, follow-up study, incidence, ICD-9

Introduction

Several studies concerning the long-term outcome of schizophrenia have been reported in Japan. However, in most of these studies, methodological problems (e.g., study population selection, methods of defining and

collecting information, diagnostic criteria, research methods, etc.) have limited researchers' ability to interpret and generalize from the results¹⁾. Outside of Japan, few studies have assembled incidence cohorts for follow-up and longitudinal study. WHO has intensified its schizophrenia research program and has initiated a set of international studies that have confirmed a different course and outcome in developing versus developed countries and explored possible reasons for these differences. The International Study of Schizophrenia (ISoS)²⁾, in which most center samples are incidence cohort, provides an opportunity to examine the full array of differences in schizophrenic patients. The authors participated in this ISoS study as a member of the DOSMeD Centers and carried out a 15-year follow-up in 1994-1995.

Methods and Subjects

Original DOSMeD cohort

The original members of the study cohort were selected according to DOSMeD protocol^{3,4)}. From January 1, 1979, to December 31, 1980, collaborating researchers interviewed all new patients who visited any of the 30 institutions participating in the study and who met specified inclusion criteria. There were 107 subjects (male, 61; female, 46). The procedure used for case selection was epidemiologically accurate enough to enable the incidence rate of schizophrenia in Nagasaki to be calculated. The procedure for case selection of new schizophrenic patients has been reported in detail⁵⁾.

Case-finding for ISoS

In 1984-1985 and 1990-1991, Nagasaki Centre carried out 5-year and 10-year follow-up studies on the course and the

outcome of the same subjects as in DOSMeD. The results of these studies and various information collected at that time (e.g., the location of subjects' residences, hospitals/clinics, etc.) were useful in tracing the subjects for this ISoS study.

Subjects under treatment were easily found for this study because most of them had not changed psychiatrists. Patients who had changed hospitals/clinics were also easy to find because information was available as to which institution they had been admitted to. Collaborating researchers explained to the psychiatrists of patients under treatment the purpose, method and importance of the project, and asked if interviewing a patient in person would have an adverse effect on the patient's condition or on the relationship between the patient and the psychiatrist. Next, the researchers asked psychiatrists to contact their patients.

For subjects who had discontinued treatment, researchers asked psychiatrists to assess the influence of interviews on their former patients as above. The psychiatrists or the collaborating researchers communicated with subjects and/or their families, who gave consent.

For subjects in no need of treatment or whose whereabouts were unknown, researchers tried to communicate with those family members who would have known about psychiatric services that subjects used to receive by using the records of psychiatric institutions that subjects had visited last, with the consent of psychiatrists in charge. Maps and public telephone books listing family names were searched. In order to protect privacy, researchers telephoned families directly.

Use of study instruments

A set of instruments was used to assess information on the subjects: Present State Examination (PSE)⁶ for evaluating symptomatology of the past month; Schedule for Assessment of Negative Symptoms (SANS)⁷ for assessing negative symptoms; Disability Assessment Schedule (DAS)⁸ for evaluating loss or restriction of the ability to carry out social roles (e.g., social withdrawal, self-care, social roles, etc.); Psychological Impairment Rating Schedule II (PIRS-II) for bridging between the PSE and the DAS; Broad Rating Schedule (BRS) with Global Assessment of Functioning Scales (GAF) for evaluating symptoms (GAF-S) and disability (GAF-D) that were modified from DSM-III-R; Substance Abuse Schedule (SAS) for obtaining information on substance abuse, including alcohol intake; Life Chart Schedule (LCS) for assessing the pattern of course in symptoms, work, residence and treatment; Family Interview Schedule (FIS) for recording information on selected familial and cultural factors and for measuring relatives' perceptions (e.g., symptoms, the cause of the illness, the stigma, the impact on the relatives' lives, etc.); and other schedules, such as

Schedules for Patients Who Refuse to Be Interviewed (RS) and Schedule for Deceased Patients (DP).

All of the interviews were given by psychiatrists who had performed the reliability exercises for the assessment instruments of this study.

Results

1. Baseline and short-term follow-up

Study population (Table 1)

The number of the original subjects of the DOSMeD at the Nagasaki Center was 107 (61 males and 46 females). In the ISoS study, among them, 7 subjects (4 males and 3 females) died, 43 subjects (28 males and 15 females) were lost to follow-up and 57 (29 males and 28 females) were successfully traced.

Table 1. Study Population-Sex and Age

	Living		Lost to Follow-up		Original DOSMeD	
	N	mean±S.D.	N	mean±S.D.	N	mean±S.D.
Male	29	24.8±7.7	28	25.7±7.2	61	24.8±7.5
Female	28	26.4±9.1	15	26.9±7.2	46	27.0±8.9
Total	57	25.6±8.5	43	26.1±7.2	107	25.8±8.2

Sex and age

There were more males than females among the original DOSMeD subjects (male: female ratio = 1.33). Among the cases lost to follow-up, the difference was greater, and the ratio of male to female being 1.87. The percentage of subjects who were lost to follow-up was 33% (15/46) in females and 46% (28/61) in males. In other words, about half the original male subjects were lost to follow-up in this study. However, this difference in sex between living cohort and the subjects lost to follow-up was not statistically significant.

Fourteen subjects (68%) out of the original subjects whose birth years were 1940-1949 were lost to follow-up. The age distribution of the subjects who were lost to follow-up was somewhat older than that of the original subjects and the successfully traced subjects, but not significantly.

Mode of onset and diagnosis

Among the original DOSMeD subjects, the number of subjects with the mode of onset "insidious, greater than one month" was large. Of 34 subjects with insidious onset, 25 (74%) were successfully traced for the ISoS. Of 19 subjects with acute onset, 12 (63%) were traced. Of 27 subjects with sudden onset or precipitous onset, 16 (59%) were traced. There was a tendency, but not a statistically significant difference, for subjects with more acute onset

to be more difficult to follow up.

Thirty-nine (68%) of the follow-up cohort of 57 subjects received a baseline diagnosis of schizophrenia, using the conversion of ICD-9 to ICD-10. For only 28% (16 subjects) of the alive group, the baseline diagnosis was "non-schizophrenia psychotic disorders (e.g., schizoaffective, acute schizo like, other psychotic)." This distribution is quite similar to that seen in both the original study cohort and those lost to follow-up (Table 2).

Table 2. Baseline Re-Diagnosis by ICD-10

	Living		Lost to Follow-up		Total	
	N	%	N	%	N	%
Schizophrenia	39	68	26	61	70	65
Schizoaffective	1	2	0	0	1	1
Acute schizo like	11	19	7	16	20	19
Bipolar/Depression	0	0	0	0	0	0
Other psychotic	4	7	5	12	9	8
Other non-psychotic	2	4	5	12	7	7
Total	57	100	43	100	107	100

Table 3. Short-Term Pattern of Course

	Living		Lost to Follow-up		Total	
	N	%	N	%	N	%
Complete remission	16	29	6	24	22	26
Incomplete remission	20	36	10	40	32	38
Continuously psychotic	19	35	9	36	31	37
Total	55	100	25	100	85	100
Missing/Other	2	—	18	—	22	—

Table 4. Severity of Symptoms

GAF Scale (Symptom)	Modified Bleuler Scale				
	N	%	N	%	
—50	16	28	Severe	7	12
51—70	24	42	Moderately	19	33
71+	17	30	Mild	15	26
			Recovered	16	28
Total	57	100		57	100

GAF Scale and Modified Bleuler Scale are provided in the BRS.

Pattern of course at early follow-up

Subjects with continuous psychotic course during the early 2-year follow-up comprised 35% (19 subjects) of the living cohort. It was not easy to compare early course between the living subjects and the subjects lost to follow-up because of much missing data for the subjects lost to follow-up. Excluding subjects with missing data or with inadequate information (Table 3), no significant differences were seen in early course between subsamples (living vs. lost to follow-up).

Because of the difference in the duration of symptom evaluation period, we could not simply compare severity of symptoms among different cohorts (deceased, lost to follow-up and living), but it bears mentioning that there

were no subjects with severe symptoms in the lost to follow-up group. In the living group, severity of symptoms ranged widely from "severe symptoms" to "recovered."

2. Living subjects: symptoms, course of illness

Symptomatology

A rather different view of current symptoms was gained from the results of the Global Assessment of Functioning Scale for symptomatology (GAF-S). Seventeen subjects (30%) showed no significant or only mild symptoms (GAF-S scores greater than 70) which coincides with the percentage of subjects recovered from symptoms on the Bleuler Scale, 28% (Table 4). However, the same percentage of subjects suffered from serious symptoms (GAF-S scores below 51).

The percentage of subjects with the most predominant symptoms in the early 1/3 of the 15-year follow-up period was about 50% (29 subjects). However, the percentage of subjects with the most predominant symptoms in the last 1/3 of the follow-up period was 12% (7 subjects).

Course of illness

Fourteen (25%) of the 57 living subjects had no psychotic episodes during the last 2 years; 9 (16%) were episodic; and 31 (54%) were continuously psychotic. Through the entire period, 25 subjects (44%) had a continuous course, which was similar to the course in the last 2 years. The overall time trend was evenly divided in thirds: 20 (35%) were getting better, 18 (32%) were the same and 19 (33%) were worse. Course typing related to relapse and type of remission was reported in another paper⁹.

3. Living subjects: residential and functional status

Living arrangements

Subjects were currently living either in a hospital (19 subjects; 33%) or with their families (35 subjects; 61%). There were no subjects living in supervised residences or nursing homes. Therefore, about 1/3 of the successfully traced subjects were still in the hospital.

Forty-one subjects (72%) had been living independently for more than 1 year during the last 2 years. Fourteen subjects (25%) had never been independent during the last 2 years and were in a hospital. No differences were seen in the duration of independent living between sex and age groups. (In this study, "live independently" means to live not in facilities such as hospitals or supervised residencies, but with family, friends, or alone in the community.)

Twenty-seven subjects (47%) had been in a hospital for some period during the last 2 years, and about half (15/27) of those subjects had been in a hospital for more than 1

year (Table 5).

No subjects had been homeless or vagrant in the last 2 years. One subject was detained at a police station for 1 day for violence.

Over the entire follow-up period, nearly all (98%) of the subjects had some experience with independent living, but 13 (23%) had lived independently for fewer than 7 years (half of the entire period). Only 16 subjects (28%) had lived independently for more than 95% of the entire period. Fifty-one (90%) subjects had experienced hospitalization. One-fourth of them (13/51) had been in a hospital for more than half of the entire period (Table 5).

No subject had been homeless through the entire period, but 1 subject had left home for a few days without telling her family.

Two subjects had been detained at a police station at some time during the follow-up period. One of them, mentioned above, was committed involuntarily to a hospital. The other subject was detained for a few days at a police station under suspicion of indecent behavior toward a child, but was released. In these cases, it was considered that the subjects' conduct was due to psychiatric symptoms. No subject was arrested or put on trial.

Work

Twenty-three subjects (40%) had worked at paid jobs at some point in the last 2 years; most (15/23) of them did so for at least 12 months. For those working most of the time, performance was mostly (77%) judged as "good" to "very good."

Thirteen (46%) of the 28 successfully traced female subjects engaged mainly in housework, 10 (36%) were employed and 6 were both employed and in housework. In total, then, 17 (61%) of them had engaged in some kind of work, while only 13 (45%) of the 29 successfully traced male subjects had been engaged in work. However, among the subjects engaged in housework for more than one year, 44% of them were evaluated as "poor" or "very poor" in their performance level.

The percentage of subjects evaluated as "good" in their global performance of work/housework in the last 2 years was 30% (14/47), while the percentage of subjects evaluated as "poor" was 53% (25/47).

In the last 2 years, there were no retired or student subjects. Twelve subjects (21%) were on a pension for mental disabilities; none received a pension for physical disabilities.

Global work performance of those who had been employed or engaged in housework during the last 2 years was rated as "good" in half of the cases (22/47).

Social disability (Table 6)

Thirty-three subjects (58%) were rated "poor" to

Table 5. Stay in Hospital

Last Two Years of Follow-up Period			Entire Period		
Months in Hospital	N	%	% Time in Hospital	N	%
Never	30	53	Never	6	11
≤12 Months	12	21	≤5 %	11	19
13-23 Months	2	4	6-10 %	11	19
24 Months	13	23	11-25 %	7	12
			26-50 %	9	16
			>50 %	13	23
Total	57	101		57	100

Table 6. Social Disability

GAF Scale (Disability)		Global Evaluation (DAS)			
	N	%	N	%	
-50	28	49	Severe	24	4
			Very Poor	12	21
51-70	6	11	Poor	19	34
			Fair	9	16
71+	23	40	Good	8	14
			Excellent	6	11
Total	57	100		56	100
			Data Missing	1	-

"severe" on the DAS in their overall functioning in the last month, while 28 (49%) had scores on the GAF-D of lower than 51, indicating serious impairment. At the same time, 23 subjects (40%) were rated "fair" to "excellent" on the DAS, and 23 subjects (40%) scored higher than 70 on the GAF-D, indicating good functioning.

The percentage of subjects for whom disability had been predominant during the early 1/3 of the period was 39% (22 subjects), while 21% (12 subjects) had disability throughout the entire period.

Violence and suicide

Assaults were committed by 12 subjects (21%) in the last 2 years, most (92%) of which were mild, except for 1 slightly more severe case. Throughout the entire period, 23 subjects (41%) committed assaults once or more, but all cases were mild (96%), except for the 1 case already noted above.

There had been only 1 mild suicide attempt in the last 2 years. Throughout the entire period, 12 subjects (21%) made at least one suicide attempt; 8 were mild, 3 moderate, and 1 was severe.

4. Living subjects : treatment status

Medications

In the last 2 years, 52 subjects (91%) had received treatment using neuroleptics ; only 4 subjects (7%) received no medication. All the subjects received neuroleptics for some or all of the entire period. This indicated wide utilization of neuroleptics. Also, most (61%) of the subjects received some kind of medication throughout the entire period.

Hospitalization

As mentioned earlier, 27 subjects (47%) had spent some time in a hospital in the last 2 years of follow-up (Table 5). Fifty-one (90%) did so at least once during the entire follow-up period. In 21 subjects (37%), hospitalization was predominant in the first 1/3 of the period, while for 11 subjects (19%) it was predominant in the last 1/3 of the period.

5. Deceased subjects

At the time of this follow-up, 7 subjects had been confirmed as having deceased. Comparison to the general population of Nagasaki Center shows an increased death rate (SMR = 5.71). Four had committed suicide : 2 by drowning and submersion (a man and woman, aged 30 and 27 at the time of death, respectively); one by intentional self-harm with a sharp object (a woman, aged 45), and one by jumping from a high place (a man, aged 28). There was also one suspected suicide case (a man, aged 31) of drowning in a bathtub after taking an excessive amount of medicine, but it was not clear if the subject had had suicidal intent.

Five of the 7 deceased subjects were in a psychotic episode at the time of their death. One was in partial remission, and the mental health status of the other was unknown.

Suicide rates in Japan were between 16 and 20 per 100,000 from 1980 to 1990. The rates in the 20s-to-50s age range were between 15.7 and 27.3 per 100,000 (1982). Compared to that of the general population, the suicide rate among our subjects, 4 or 5 suicide cases out of 107 subjects, is extremely high.

Discussion

This study is the first report in Japan on long-term follow-up of incident cohort of schizophrenia with pre-defined reliable criteria for obtaining subjects and evaluating symptoms, disabilities, course and outcome. Unfortunately, many subjects (40%) were lost to follow-up. The representativeness of the living cohort was not

complete but permissible because the characteristics (e.g., more acute onset, male predominance, milder symptoms, older age distribution) of the subjects lost to follow-up were slightly different (but not to a statistically significant extent) from those of the living cohort. The subjects lost to follow-up were similar at diagnostic distribution, short-term course type.

Mortality rate among the subjects was far higher than that of the general population. The high suicide rate in particular is an issue of great importance for long-term treatment and care. Also, clinicians should pay attention to even mild suicide attempts, which were commonly seen (21%) during the long-term course in patients with schizophrenia.

Severity of subjects' symptoms at the 15-year follow-up varied widely, from "severe" to "remission." Social disability also differed from patient to patient. The variety of symptomatological and social outcome showed the heterogeneity of schizophrenia ; many types exist, with many possible courses and outcomes. The authors reported¹⁰ that subtyping of schizophrenia at baseline by using the International Classification of Diseases 10th Revision-Diagnostic Criteria for Research (ICD-10/DCR), a set of operational diagnostic criteria, could predict the difference in outcome between hebephrenic and paranoid schizophrenia.

The overall outcome of the living subjects (good, 40% ; poor, 55%) was consistent with the results of previous studies with using 10-to-20-year follow-up periods in which good outcome was reported in 37% - 58% of the subjects^{11, 12, 13, 14}. The limitations of our case-finding method may have prevented us from finding better-outcome subjects, such as those who no longer needed treatment due to remission or "recovery."

The overall time trend (getting better, the same, and worse) was almost evenly divided in thirds. Some of the patients with schizophrenia displayed continuous course and poor outcome ; however, the present study--a methodological, highly structured prospective cohort study--indicates that the outcome of schizophrenia is not always poor.

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study of characteristics of mental disorders and their course in different settings, and to strengthen the scientific basis for future international multidisciplinary research on schizophrenia and other psychiatric disorders seen in a public health perspective.

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