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Heterogeneity of Schizophrenia and ICD-10 Subclassification System

Keiko SAKAI, Hitoshi MATSUMURA, Shigenori TERASHIMA**, Jun SAKAI, Shin-ichiro MIYAZAKI, Rumiko SEGAWA*, and Hiroyuki ASABA

*Department of Neuropsychiatry, *Nursing division, Osaka Medical College, 2-7 Daigakumachi, Takatsuki City, Osaka 569 ; and **Department of Psychology, Kansai University, Suita, Osaka 564, Japan*

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ABSTRACT

MITSUDA demonstrated in 1942 the heterogeneity of schizophrenia and identified a disease entity for which he coined the term "atypical psychosis". He pointed out the importance of genetical factors for differentiating atypical psychosis from schizophrenia.

To examine the clinical validity of ICD-10, we studied 60 patients with either schizophrenia or schizotypal and delusional disorders, assuming that F20 corresponds to typical schizophrenia, and that F23 and F25 accord with atypical psychosis. The patients' symptoms, clinical course and intrafamilial psychopathological traits were classified into 28 categories and analyzed with HAYASHI's multivariate analyses.

The study showed that the subclassification system of ICD-10 clearly separated a group of 34 patients with atypical psychosis and another group of 26 with typical schizophrenia. The most important differentiating factor was intrafamilial psychopathological traits. These findings conform to MITSUDA's concept. However 4 patients in the atypical psychosis group had a trait of schizophrenia, indicating that F23 and F25 include not only patients with atypical psychosis, but also schizophrenic patients.

MITSUDA's differentiating diagnosis was based on a nosological concept with consideration of hereditary aspects, whereas ICD-10 is symptom oriented. As our results indicate, the subclassification system of schizophrenia in ICD-10 needs further modification with particular regard to genetical aspects.

INTRODUCTION

Schizophrenia is one of the most elusive diseases, consisting of heterogeneous subgroups. MITSUDA (1942) demonstrated the heterogeneity of schizophrenia by conducting clinico-genetical studies. His concept was further developed thereafter, leading to differentiation of a disease entity for which he coined the term "atypical psychosis".

Typical schizophrenia, defined by MITSUDA (hereafter typical schizophrenia), is characterized by an insidious onset without a precipitating factor, a chronic course with progressive deterioration of personality, and monomorphous symptoms. MITSUDA's atypical psychosis (hereafter atypical psychosis) is characterized by an acute or subacute onset with precipitating factors, polymorphous symptoms, an episodic course with complete or social remission with residual symptoms. MITSUDA (1979) attributed typical schizophrenia to pathology of personality, and atypical psychosis to pathology of consciousness. Ac-

cording to MITSUDA (1954), no family member of a proband with typical schizophrenia was diagnosed as having atypical psychosis and *vice versa*. Furthermore, the same was the case for the co-twin of a patient with atypical psychosis, as well as of a patient with typical schizophrenia (MITSUDA and SAKAI, 1968). Thus, typical schizophrenia and atypical psychosis were shown to be nosologically distinct disease entities, and this conclusion was further confirmed by others (HATOTANI, 1955 ; KUROSAWA, 1962 ; TSUANG et al., 1976 ; and TSUANG, 1982).

World-wide efforts have been made to devise an internationally acceptable standard of diagnosis. Currently the most commonly used standard is ICD-10 classification of mental and behavioral disorders (WORLD HEALTH ORGANIZATION, 1990) which the Japanese Ministry of Health and Welfare recommends for use in routine clinical settings. Although the ICD classification system has been revised 10 times, it is still not without flaws.

In the present study, we examine the clinical validity of the subclassification system of schizophrenia in ICD-10 with particular consideration of genetical aspects.

SUBJECTS and METHODS

The MENTAL HEALTH SERVICES RESEARCH FUND of JAPANESE MINISTRY of HEALTH and WELFARE (1990) established a modified version of ICD-10 for use in Japan and devised a subgroup of atypical psychosis which includes F23 (acute and transient psychotic disorders) and F25 (schizoaffective disorders). On the basis of this classification, we assumed that F23 and F25 correspond to atypical psychosis and F20 (schizophrenia) to typical schizophrenia.

Between June 1991 and December 1995, the first author treated 92 psychiatric patients at the Department of Neuropsychiatry, Osaka Medical College Hospital and Han-nan Psychiatric Hospital which is an affiliated hospital of Osaka Medical College. Thirty patients were males and 62 were females. Of these 92 patients, 60 were subclassified to one of the following subdiagnoses : F20 (schizophrenia : F20.0, F20.1, F20.3, and F20.6), F23 (acute and transient psychotic disorders : F23.0, F23.1, F23.3, and F23.8) and F25 (schizoaffective disorders : F25.0 and F25.1) in ICD-10 (**Table 1**). Of these 60 patients, 18 were males and 42 females. Twenty-six patients belonging to F20 were subclassified in Group 1 (typical schizophrenia group), and 34 patients belonging to F23 and F25 were subclassified in Group 2 (atypical psychosis group). Each patient had been observed for more than 3 years. The remaining 32 patients did not fulfill the criteria of F20, F23 and F25.

Table 1 Distribution of patients among categories of ICD-10

Categories	number of patients
Paranoid schizophrenia (F20.0)	19
Hebephrenic schizophrenia (F20.1)	3
Undifferentiated schizophrenia (F20.3)	2
Simple schizophrenia (F20.6)	2
Acute polymorphic psychotic disorder without symptoms of schizophrenia (F23.0)	10
Acute polymorphic psychotic disordes with symptoms of schizophrenia (F23.1)	5
Other acute predominantly delusional psychotic disorders (F23.3)	2
Other acute and transient psychotic disorders (F23.8)	4
Schizoaffective disorder, manic type (F25.0)	4
Schizoaffective disorder, depressive type (F25.1)	9
Total	60

Information was obtained from the patients and their family members concerning 28 categories of investigation. These 28 categories were based on MITSUDA's 53 items of investigation, which were revised to 64 categories. Of these, 36 categories were omitted from our investigation because the incident rates of these were low. The list of categories is presented in **Table 2**.

The first-degree relatives i.e. parents, children, and siblings and the second degree relatives i.e. grandparents, uncles, and aunts were examined for intrafamilial psychopathological traits. When one or more family members were diagnosed as having a mental disorder, that particular disorder was considered to be the trait of that family. When two or more mental disorders coexisted in the same family, only the diagnoses ascertained by the first author were taken as the intrafamilial psychopathological trait ; and priority was given to the traits found in the first-degree relatives.

Table 2 Categories of investigation

1) Intrafamilial psychopathological traits	(typical schizophrenia. atypical psychosis, mood disorders, neurosis, epilepsy, alcoholrelated disorders, personality disorders, mental retardation, organic mental disorders, no pathological traits)
(Objective symptoms)	
2) Disturbed affective rapport	(insufficient, reserved)
3) Disturbed formal rapport	(insufficient, reserved)
4) Disturbed countenance	(rigid, cold, bland, distorted)
5) Disturbed posture	(rigid, stereotype, manneristic, bizarre)
6) Disturbed behavior	(negativistic, echo-symptom, cataleptic)
7) Disturbed behavior	(impulsive, hyperkinetic, excited)
8) Disturbed thought	(blocking, splitting, monologue)
9) Disturbed thought	(slow, circumstantial, inhibited)
10) Disturbed affect	(monotonous, vacant, indifferent, ambivalent)
11) Disturbed emotion	(irritable, agitated, anxious)
12) Disturbed mood	(unstable, manic, depressive)
13) Disturbed memory	(amnesia, perverted recall)
14) Disturbed apprehension and attention	(miscomprehension, inattentive)
(Subjective symptoms)	
15) Experience of being influenced	(feeling of being influenced, feeling of being deprived of thought)
16) Experience of being influenced	(experience of being interfered with, somatic experience of being influenced)
17) Hallucination	(sensory-conceptual)
18) Auditory hallucination	(verbal-elementary, presence or absence of self-reference)
19) Verbal hallucination	(human voice, acquainted or unacquainted, imperative, interfering)
20) Visual hallucination	(sensory-elementary)
21) Delusional perception, delusional feeling	(experience of meaningfulness)
22) Delusion	(systematic-fragmental)
23) Delusion of persecution	(delusion of reference, observation)
24) Suicidal idea and attempt	
25) Vegetative symptoms	
(Types of onset and course)	
26) Precipitating factor at onset	(physical, mental, social)
27) Onset	(gradual, subacute, acute)
28) Course of illness	(chronic, episodic, periodic)

i) Data of individual patients were analyzed by use of HAYASHI's third method of quantification, which enables us to group individuals with similar symptoms (HAYASHI, 1952).

ii) The categories of investigation were analyzed by use of HAYASHI's third method of quantification, which enables us to clarify how closely the clinical symptoms and intrafamilial psychopathological traits are related.

iii) The categories of investigation were also analyzed by use of HAYASHI's second method of quantification (HAYASHI, 1967), which selects the most effective categories to differentiate two groups.

All patients and families gave informed consent prior to the study. Mean values are presented with ±S.D. If the variances were equal (F-test), comparisons between Groups 1 and 2 were carried out with Student's *t*-test. If the variances were unequal (F-test), comparisons were carried out with Welch's *t*-test. Chi-square was used to test the gender ratio between Groups 1 and 2.

RESULTS

The mean ages at the time of investigation and of the onset at illness of the 2 groups did not differ significantly by Student's *t*-test (**Table 3**). The mean duration of admission to a psychiatric hospital was significantly greater in Group 1 than in Group 2 by Welch's *t*-test ($p<0.05$). Group 2 patients were admitted more frequently than Group 1 by Student's *t*-test ($p<0.05$) (**Table 4**).

Table 3 Ages at the time of investigation and onset of illness

Time of \ Diagnosis	Group 1	Group 2
Investigation	34.5±14.1	37.7±12.6
Onset	26.7±10.1	28.4±11.9

Table 4 Duration and frequency of admission

Admission \ Diagnosis	Group 1	Group 2
Duration (months)	5.8±6.9	3.3±2.8*
Frequency	2.4±2.7	3.9±3.5□

*$p<0.05$ by Welch' t-test
□$p<0.05$ by Student's t-test

The gender ratio was not significantly different between Groups 1 and 2. The number of females was greater than that of males in both groups.

i) Data of individual patients were analyzed by use of HAYASHI's third method of quantification, and 2 clusters were distinctly differentiated (**Figure 1**). Cluster 1 was composed of Group 1 patients ; and Cluster 2, of Group 2 patients.

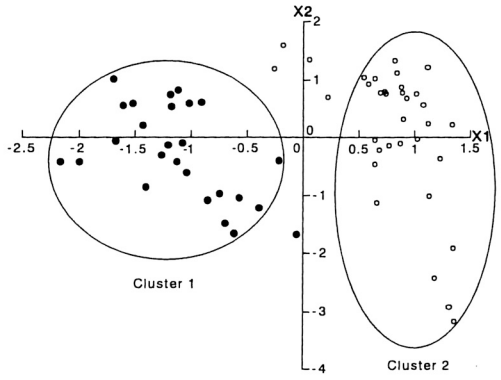

Fig. 1. Scatter diagram indicating the distribution of datum points, which stand for the X1 (abscissa) and X2 (ordinate) values calculated for individual patients by HAYASHI's third method of quantification
Datum points corresponding to the patients of Group 1 are represented by closed circles, and those corresponding to the patients of Group 2 are shown by open circles. Clusters 1 and 2 are encircled by lines.

ii) Data of the 28 categories (**Table 2**) were also analyzed by HAYASHI's third method of quantification, which separated out a further 2 groupings, i. e. Cluster A and Cluster B (**Figure 2**). Clusters A and B, corresponded to Clusters 1 and 2, respectively. Cluster A consisted of categories 4 (rigid and cold countenance), 5 (rigid and bizarre posture), 6 (negativistic behavior), 8 (monologue), 10 (flattening of affect), and 28 (chronic course). Cluster B consisted of categories 2 (disturbed affective rapport), 11 (irritation and anxiety), 12 (manic-depressive mood), 13 (amnesia), 14 (disturbed apprehension and attention), and 20 (visual hallucination).

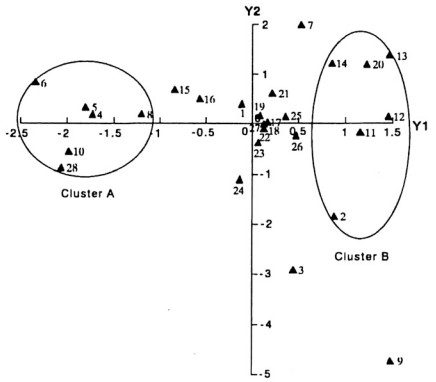

Fig. 2. Scatter diagram indicating the distribution of datum points, which stand for the Y1 (abscissa) and Y2 (ordinate) values calculated for individual categories (listed in the Table 2) by HAYASHI's third method of quantification
The numbers close to the respective datum points indicate the category numbers described in Table 2. Clusters A and B are encircled by lines, corresponding to the Clusters 1 and 2, respectively, of Fig. 1.

iii) Analysis by use of HAYASHI's second method of quantification revealed that categories 1 (intrafamilial psychopathological traits), 27 (type of onset), 10 (disturbed affect), 2 (disturbed affective rapport), 14 (disturbed apprehension and attention), and 28 (course of illness) were discriminating factors. Among these, category 1 was the most reliable discriminating factor between Groups 1 and 2 (**Table 5**).

Thirteen patients in Group 1 (50%) and 17 in Group 2 (50%) had intrafamilial traits of mental disorders (**Table 6**). Major traits in Group 1 were of schizophrenia, personality disorders, and mental retardation ; the trait of atypical psychosis was not detected. Traits seen in Group 2 were traits of schizophrenia, atypical psychosis, neurosis, alcohol-related disorders,

and mental retardation. Traits of epilepsy and organic mental disorders were not found in either group.

Table 5 Partial correlations

No.	Categories	Partial correlations
1	Intrafamilial psychopathological traits	0.903
27	Onset	0.897
10	Disturbed affect	0.895
2	Disturbed affective rapport	0.889
14	Disturbed apprehension and attention	0.859
28	Course of illness	0.855
22	Delusion	0.803
3	Disturbed formal rapport	0.794
7	Disturbed behavior	0.788
4	Disturbed countenance	0.776
5	Disturbed posture	0.719
15	Experience of being-influenced	0.701
13	Disturbed memory	0.686
23	Delusion of persecution	0.673
9	Disturbed thought	0.653
11	Disturbed emotion	0.615
20	Visual hallucination	0.573
16	Experience of being-influenced	0.550
24	Suicidal idea and attempt	0.481
25	Vegetative symptoms	0.476
8	Disturbed thought	0.471
12	Disturbed mood	0.455
19	Verbal hallucination	0.369
6	Disturbed behavior	0.323
18	Auditory hallucination	0.208
17	Hallucination	0.158
26	Precipitating factor at onset	0.097
21	Delusional perception, delusional feeling	0.091

Table 6 Intrafamilial psychopathological traits

Psychopathological traits	Group 1	Group 2
Typical schizophrenia	3 (11.5%)	4 (11.8%)
Atypical psychosis	0 (0.0%)	2 (5.9%)
Mood disorders	1 (3.8%)	1 (2.9%)
Neurosis	2 (7.7%)	4 (11.8%)
Epilepsy	0 (0.0%)	0 (0.0%)
Alcohol-related disorders	0 (0.0%)	3 (8.8%)
Personality disorders	4 (15.4%)	1 (2.9%)
Mental retardation	3 (11.5%)	2 (5.9%)
Mental organic disorders	0 (0.0%)	0 (0.0%)

DISCUSSION

In the present study, we found no statistically significant gender difference between Groups 1 and 2. However, there was a large bias in our population towards female participants not consistent with the incidence of schizophrenia in society at large. Therefore, we should not draw any conclusion with regard to gender ratio. The mean ages at the time of investigation and at the onset of illness did not differ between Groups 1 and 2. The frequency of hospital admission was greater in Group 2 and the duration of admission was greater in Group 1, in keeping with our clinical impression.

HAYASHI's third method of quantification (HAYASHI, 1952) differentiated Clusters 1 and 2 (**Fig. 1**) which corresponded to Group 1 (F20) and Group 2 (F23 and F25), respectively. This result supports the validity of F20, F23 and F25 of ICD-10. The 28 categories were also grouped into Clusters A and B (**Fig. 2**), corresponding to Clusters 1 and 2 (**Fig. 1**). Therefore, the categories included in Cluster A were associated with Group 1, and the categories included in Cluster B were related to Group 2. Group 1 patients were characterized by negativistic behavior, disturbed countenance, disturbed posture, monologue, flattening of affect, and chronic course. Group 2 patients had features of disturbed affective rapport, irritation, anxiety, disturbed mood, amnesia, visual hallucination, and disturbed apprehension and attention.

Analysis with HAYASHI's second method of quantification (HAYASHI, 1967) showed that the categories of intrafamilial psychopathological traits, type of onset, disturbed affect, disturbed affective rapport, course of illness, and disturbed apprehension and attention, contributed to differentiate Groups 1 and 2 (**Table 5**). Intrafamilial psychopathological trait was the most important category in separating the 2 groups.

MITSUDA et al. (1966) previously demonstrated that patients with typical schizophrenia and those with atypical psychosis could be differentiated by use of factor analysis with 53 items of investigation. They showed that the features of typical schizophrenia were gradual onset, emotional blunting, chronic course, personality deterioration, disturbed countenance, disturbed rapport, and disturbed posture ; whereas, the features of atypical psychosis were impaired consciousness, incoherence, amnesia as to pathological experiences, periodic

and phasic course, insight into illness at recovering stage, disturbed orientation, delusional perception, drowsy countenance, and disturbed apprehension and attention. Our findings are in keeping with MITSUDA's results as there were 2 distinct subgroups in schizophrenia, despite minor differences between MITSUDA's discriminating factors and ours. Our study showed that intrafamilial psychopathological trait was the most important category in separating atypical psychosis from schizophrenia, as MITSUDA indicated (1954).

In this study, we assumed that F20 (Group 1) corresponded to typical schizophrenia, and that F23 and F25 (Group 2) corresponded to atypical psychosis. We could discriminate Group 1 and Group 2 by HAYASHI's third method of quantification. However Groups 1 and 2, subclassified according to ICD-10 were not identical with typical schizophrenia and atypical psychosis described by MITSUDA.

MITSUDA (1954, 1979) ascertained a strong homotypic trait of typical schizophrenia and of atypical psychosis, concluding that typical schizophrenia and atypical psychosis were genetically and nosologically separate disease entities. However, in the present study 4 patients in Group 2 had an intrafamilial psychopathological trait of typical schizophrenia. Among the 4 patients in Group 2 (atypical psychosis group), whose families had a trait of typical schizophrenia, 2 were subclassified into F23.0 (acute polymorphic psychotic disorder without symptoms of schizophrenia) and the remaining 2 were subclassified into F25.0 (schizoaffective disorder, manic type). All 4 had hallucinations and delusions, but did not fulfill the criteria of schizophrenia in ICD-10. The common characteristics of these 4 patients were : age at onset between 17 and 19 ; childish and inappropriate behavior as residual symptoms ; inability to cope with social life, difficulty in finding a marriage partner and failure to maintain a normal married life ; and inability to hold a single job for a long time. These characteristics are features of typical schizophrenia rather than of atypical psychosis. Had the 4 patients been diagnosed according to the concept of MITSUDA and SAKAI (MITSUDA and SAKAI, 1968 ; MITSUDA, 1979), they would have been included in the group of typical schizophrenia patients. These findings indicate that F23 and F25 of ICD-10 include not only patients with atypical psychosis, but also typical schizophrenia patients. In the 32 patients who were excluded from this study, we found no patients with MITSUDA's typical shiczophrenia ; however, we found 3 patients with MITSUDA's atypical psychosis. These 3 patients belonged to the category of mood disorders of ICD-10.

Our results showed that F23 and F25 of ICD-10 correspond symptomatologically to atypical psychosis ; however, these subclasses do not correspond to atypical psychosis on a genetical basis. MITSUDA (1954) found that atypical psychosis patients had the intrafamilial psychopathological traits of a homotype of atypical psychosis as well as traits of epilepsy, and manic-depressive disease. We found 7 traits in the family members of patients with atypical psychosis as shown in **Table 6** ; they included the trait of typical schizophrenia. Our results did not show the homotype of atypical psychosis.

Differentiation between typical schizophrenia and atypical psychosis made by MITSUDA et al. was based on a nosological concept with consideration of hereditary aspects, whereas the subclassification system of ICD-10 for schizophrenia is symptom oriented. Our study showed that the Japanese version of ICD-10 subclassification clearly separated atypical psychosis and typical schizophrenia, and that the most important differentiation factor was intrafamilial psychopathological traits. These findings conform to MITSUDA's classification. However, we found 4 of 34 patients diagnosed according to ICD-10 as having atypical psychosis had the intrafamilial trait of typical schizophrenia, contradicting MITSUDA's concept.

Theoretically, the diagnosis of schizophrenia should be established on the basis of symptomatology, course of illness, outcome and intrafamilial psychopathological traits. As the present study indicates, the subclassification of schizophrenia in ICD-10 needs further modification with particular consideration of genetical aspects.

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