Eur Arch Psychiatry Clin Neurosci (1991) 240:250–254

European Archives of Psychiatry and Clinical Neuroscience

A Prospective Study of Tardive Dyskinesia in Japan

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Received March 8, 1990

Summary. A large-scale, prospective study of tardive dyskinesia (TD) was performed in 11 psychiatric facilities in Japan. A total of 1595 psychiatric patients were enrolled in this study in 1987. The progress of these patients, with the exception of 490 dropouts, has now been followed up to 1988. The prevalence of TD at study entry was 7.6%, the annual incidence rate was 3.7% and the annual remission rate was 28.7%. Newly developed TD patients tended to be older, to have undergone more psychosurgery, and to have had lower neuroleptic doses than the patients who had not developed TD, whereas no specific variable could be detected as a factor associated with remission of TD. The results suggest that the incidence of TD is lower in Japan than that in Europe and North America.

Key words: Tardive dyskinesia – Prospective study – Prevalence – Incidence – Remission rate

Introduction

It has been more than 30 years since tardive dyskinesia (TD) was first described. During this period, the treatment of TD has been extensively discussed. However, satisfactory treatment remains to be identified. The disappointing status of TD therapy has focused attention on preventive strategies. Indeed, a large number of cross-sectional studies on TD have been carried out and the results utilized to identify risk factors for TD. However, longitudinal prospective studies are essential to establish the precise risk factors. In contrast to the numerous cross-sectional studies, only a few prospective studies on TD have been performed (Kane et al. 1982, 1984, 1986; Barnes et al. 1983; Chouinard et al. 1986).

We have been studying the epidemiology and treatment of TD since the first Japanese case of TD was described by Yagi, one of our colleagues, in 1970 (Itoh 1981; Itoh et al. 1977; Yagi et al. 1976, 1989; Yagi and Itoh 1985, 1987). During this process, a large-scale prospective study on involuntary movements in psychiatric patients was begun in 1987. The present report focuses on the epidemiological features of TD in this population, during the 1st year of the prospective evaluation up to 1988.

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Methods

Participating Facilities. This prospective study on involuntary movement disorders was designed in the form of the joint study with Keio and Kyorin universities, Tokyo, Japan and initiated in 1987. Eighteen psychiatrists working in the 11 facilities participated in this survey which included eight psychiatric hospitals, psychiatric outpatient divisions in two general hospitals and one psychiatric outpatient division in a university hospital.

Subject Selection. As a rule, patients who had received psychiatric therapy from one of the psychiatrists in our research group for at least 6 months were chosen as subjects of this study. Thus, the subjects who were included suffered from most of the diseases treated in the psychiatric field. Only approximately 13% of all subjects had not received neuroleptic medications for 2 weeks prior to the first evaluation. These included patients who had (1) manifested persistent dyskinesia following neuroleptic withdrawal; (2) received neuroleptic therapy intermittently but not in this 2-week period; and (3) never received neuroleptic therapy before. The patients in the last group served as a control group. However, patients who met the following criteria were excluded: patients (1) who had manifested involuntary movements at study entry because of underlying neurological disorders; (2) whose psychiatric condition did not permit evaluation of their involuntary movements; and (3) who rejected evaluation for their involuntary movements. The clinical diagnoses (ICD-9) of the entire set of subjects included schizophrenia ($n = 1140$), mental retardation ($n = 118$), affective psychoses ($n = 94$) and others ($n = 243$).

Ratings for TD. All subjects were examined for TD and signs of parkinsonism. Tardive dyskinesia was assessed using the Abnormal Involuntary Movement Scale (AIMS), which has been trans-

lated into Japanese by our group. Inter-rater and test-retest reliabilities of this AIMS Japanese version have also been established by our group (Itoh et al. 1977). Ratings for TD were performed at individual facilities by psychiatrists in our research group. Before the initiation of this study, all raters had been specially trained in the use of the AIMS, with the use of videotaped material, until every rater could reproduce stable and precise evaluations. Patients were identified as having TD when the total AIMS score was higher than 2.

Demographic and Medical Information. The demographic and medical information of the subjects used for the data analyses were taken, retrospectively, from clinical records in as many patients as possible. These included drug therapy at study entry, total years of exposure to neuroleptics and past history of electroconvulsive therapy (ECT), insulin shock therapy (IST) and psychosurgery. Daily doses of neuroleptics and antiparkinsonian drugs in each patient, for the 2 weeks prior to the first evaluation, were calculated to yield an average daily dosage and equivalent doses of chlorpromazine and promethazine were calculated by using a table developed specifically for Japanese patients (Itoh 1985).

Table 1. Criteria for exclusion from follow-up

Reasons for failing to follow-up 490 patients	Number of patients
Factors on rater's side	
No longer working in the same hospital (3 raters)	257
Gave up attending this study (3 raters)	117
Careless leakage of the record	2
Subtotal	*376*
Factors on patient's side	
Inpatient at another hospital	32
Failed to return to the clinic	29
Discharged	27
Dead	12
Termination of the treatment	6
Home medication	3
Moved outside the Tokyo area	3
Refused follow-up examination	2
Subtotal	*114*

Period of this Survey. An initial examination, with documentation of the characteristics of TD, was performed in 1595 patients from April through September 1987. In 1988, TD was reassessed by the same psychiatrists between 11 and 13 months after the first evaluation. The prevalence of TD was calculated from the data in 1987. Incidence and remission rates were calculated from the data, in 1987, and again at the second evaluation in 1988.

Results

Of the initial 1595 patients, 1105 were re-evaluated in 1988, while 490 were lost to follow-up for a variety of reasons (Table 1). A total of 77% of all dropouts were attributable to a failure by one of the raters, while dropouts due to patient failures totalled only 23%. The characteristics of the entire population base at study entry, as well as a comparison of the characteristics between the patients who were lost to follow-up and those who remained in the study population, are shown in Table 2. Patients lost to follow-up tended to be younger, to have had fewer courses of ECT, IST and psychosurgery, to have received neuroleptic therapy for a shorter period and were receiving lower daily doses of neuroleptics and antiparkinsonian drugs.

Table 3 indicates the correlations of the severity of TD in 1987 with four demographic and medical variables, and the intercorrelations among these four variables. A relatively high correlation with the severity of TD was found in age and total years of exposure to neuroleptics. However, it should be noted that as the duration of total neuroleptic exposure increases, so does the age of the patients. In fact, a highly significant correlation was found between these two variables.

The characteristics of patients with new onset of TD were identified following a comparison with those patients who had not developed TD in 1988 (Table 4). Patients with newly developed TD tended to be older, to be more likely to have had psychosurgery and to have had a lower total neuroleptic dosage than the patients who had not developed TD.

Table 2. Study population characteristics

	Overall subjects	Follow-up cohort	Lost to follow-up	Statistical significance[a]
Number of patients	1595	1105	490	
Sex ratio (M/F)	1.31	1.25	1.47	NS
Age[b] (years)	50 ± 13	51 ± 13	48 ± 14	$P < 0.01$
History of ECT	33.8%	40.2%	18.7%	$P < 0.01$
History of IST	7.0%	8.9%	2.8%	$P < 0.01$
History of psychosurgery	8.6%	11.9%	1.4%	$P < 0.01$
Signs of parkinsonism	34.9%	36.4%	31.6%	NS
Total years of exposure to neuroleptics[b]	20 ± 9	20 ± 9	13 ± 10	$P < 0.01$
Neuroleptic dosage[c]	411	426	303	$P < 0.01$
Dosage of antiparkinsonian drugs[d]	92	95	67	$P < 0.01$

ECT, electroconvulsive therapy; IST, insulin shock therapy
[a] Difference between follow-up cohort of patients and those lost to follow-up
[b] Mean ± SD (years)
[c] Mean chlorpromazine equivalents (mg/day)
[d] Mean promethazine equivalents (mg/day)

Table 3. Correlation with the severity of tardive dyskinesia (TD)

	Severity of TD	Demographic and medical variables		
		(1)	(2)	(3)
(1) Age	$r = 0.23^b$ $n = 1592$			
(2) Total years of exposure to neuroleptics	$r = 0.17^b$ $n = 935$	$r = 0.55^b$ $n = 935$		
(3) Neuroleptic dosage	$r = 0.08^b$ $n = 1260$	$r = 0.23^b$ $n = 1260$	$r = 0.02$ $n = 935$	
(4) Dosage of antiparkinsonian drugs	$r = 0.04$ $n = 1179$	$r = 0.12^b$ $n = 1179$	$r = 0.07^a$ $n = 909$	$r = 0.39^b$ $n = 813$

Units of the above items are the same as Table 2

[a] $P < 0.05$; [b] $P < 0.01$

r, Correlation coefficient with the severity of TD in 1987; n, number of patients used in these analyses; P, the probability which occurs when the null hypothesis "$r = 0$" is postulated

Table 4. Characteristics of patients with newly developed TD

	TD(−) in 1987 TD(+) in 1988	TD(−) in 1987 TD(−) in 1988	Statistical significance
Number of patients	38	974	
Sex ratio (M/F)	1.11	1.29	NS
Age (years)	55 ± 13	50 ± 13	$P < 0.05$
History of ECT	50.0%	38.0%	NS
History of IST	13.8%	8.1%	NS
History of psychosurgery	23.7%	10.3%	$P < 0.05$
Signs of parkinsonism	38.9%	33.7%	NS
Total years of exposure to neuroleptics	22 ± 8	20 ± 9	NS
Neuroleptic dosage	249	448	$P < 0.01$
Dosage of antiparkinsonian drugs	108	95	NS

Units of the above items are the same as Table 2

Table 5 compares the characteristics of patients who recovered from TD with those of patients in whom TD symptoms had not improved up to 1988. No definitive differences of the characteristics between these two groups could be detected.

Table 6 and Fig. 1 indicate the three different epidemiological indexes of TD, i.e., prevalence in 1987, annual incidence and annual remission rate. As can be seen from Table 6, a higher prevalence of TD could be observed in female patients, in patients who had experienced ECT, IST and psychosurgery and in patients who manifested signs of drug-induced parkinsonism. A significant difference in incidence could be observed only between the patients with and without a history of psychosurgery, whereas there were no significant differences in the remission rate of TD. The most obvious tendency that can be identified from Fig. 1 was the correlation with age. As age increases, so do the prevalence and the incidence of TD. In contrast, the remission rate was found to decrease with age. No systematic relationship could be observed between TD and drug history.

Table 5. Characteristics of patients in remission from TD

	TD(+) in 1987 TD(−) in 1988	TD(+) in 1987 TD(+) in 1988
Number of patients	27	66
Sex ratio (M/F)	0.93	0.94
Age (years)	57 ± 12	61 ± 12
History of ECT	52.0%	64.3%
History of IST	14.3%	17.0%
History of psychosurgery	26.9%	21.5%
Signs of parkinsonism	70.8%	63.9%
Total years of exposure to neuroleptics	22 ± 8	23 ± 8
Neuroleptic dosage	337	240
Dosage of antiparkinsonian drugs	96	80

Units of the above items are the same as Table 2. No statistically significant differences could be detected between these two groups

Table 6. Epidemiological indexes of TD

		Prevalence in 1987	Incidence	Remission rate
Total		7.6%	3.7%	28.7%
Male		6.5%]a	3.5%	28.9%
Female		9.1%]	4.0%	28.6%
History of ECT	(+)	12.8%]c	4.7%	26.5%
	(−)	4.6%]	3.0%	37.5%
History of IST	(+)	11.8%]b	6.3%	25.0%
	(−)	6.5%]	3.6%	29.0%
History of psychosurgery	(+)	15.4%]c	8.3%]c	33.3%
	(−)	6.9%]	3.2%]	26.8%
Parkinsonism	(+)	13.9%]c	4.1%	30.4%
	(−)	3.7%]	3.3%	23.3%
Schizophrenia		8.1%	4.0%	25.0%
Affective psychoses		6.7%	1.9%	25.0%
Mental retardation		12.5%	2.9%	36.4%

[a] $P = 0.0501$, [b] $P < 0.05$, [c] $P < 0.01$

Discussion

Although a variety of cross-sectional prevalence studies of TD have been reported previously, these point-prevalence studies give less information on risk factors than do longitudinal prospective studies. A prospective study usually requires long-term, laborious observation, which may account for the relatively small numbers of incidence studies which have been performed. As summarized in Table 7, the incidence of TD which has been reported ranges from 2.9% to 11.0%. These differences are attributable to differences in the population base of each study, when and where the study was carried out

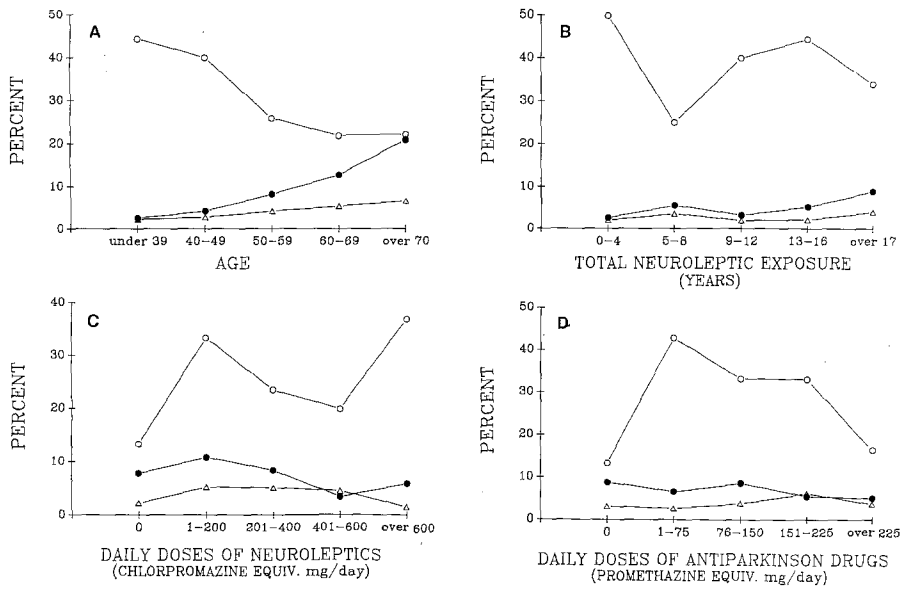

Fig. 1. Correlations between epidemiological features of tardive dyskinesia and patient characteristics. Significant differences are observed in prevalence of each divided "age" group ($P < 0.01$; χ^2; $df = 4$) and of each divided "daily doses of neuroleptics" group ($P < 0.05$; χ^2; $df = 4$). ●—● prevalence; △—△ incidence; ○—○ remission rate

Table 7. Summary of previously reported prospective studies

Reference	Population base	Observation terms	Mean age	Sex ratio (M/F)	Ratio of schizophrenia	Annual incidence	Country
Kane et al. (1982)	328	4 years	27 (± 9)	1.44	59%	2.9%	USA
Barnes et al. (1983)	182	3 years	51	?	?	11.0%	UK
Kane et al. (1984)	554	7 years	28 (± 10)	1.17	52%	3.1% (3.3%)	USA
Kane et al. (1986)	616	8 years	28 (± 10)	1.33	58%	4.3% (4.3%)	USA
Chouinard et al. (1986)	256	5 years	40	0.87	100%	2.9%	Canada
Inada et al. (present study)	1595	1 year	50 (± 13)	1.31	71%	3.7%	Japan

The mean age (± SD), sex ratios and ratios of schizophrenia shown here were calculated from published data at study entry. Annual incidence rates were recalculated from the observation terms in each study, while those in parentheses were recalculated from 4 years' data

and varying investigative methods. Kane et al. (1982, 1984, 1986) reported annual incidence rates (2.9%–4.3%) similar to those of the present study, although the population base in their study was much younger. On the other hand, Barnes et al. (1983) examined a population base with an age similar to ours, which exhibited an incidence rate of TD almost 3 times higher than ours. Although cross-sectional studies seem to have failed to detect differences in the prevalence of TD between races (Yagi 1980; Itoh 1981), the present findings suggest that the incidence of TD in Japan is lower than that in Europe and North America. Compared with the other studies listed in this table, the diagnostic criteria for TD which were used in this study are relatively mild, which should reinforce this conclusion.

A sharp contrast can be noted between the present results and the results of Binder and Levy (1981), who noted a higher incidence of acute, extrapyramidal side effects in Asian patients, including Japanese, than in white and black patients. This striking difference could be indirect evidence of different mechanisms between acute and tardive extrapyramidal reactions.

Several predisposing factors have been identified from prevalence studies. Aging is considered to be the most important and established predisposing factor (Gerlach and Casey 1988). This was substantiated by the correlation between three epidemiological indexes of age and TD (Fig. 1A). Sex (higher prevalence in female patients), brain damage and pre-existing extrapyramidal syndromes have occasionally been identified as risk factors for TD (Gerlach and Casey 1988). While patients with these characteristics showed a significantly higher prevalence of TD in the present study, this higher incidence was noted only in those patients with a history of psychosurgery (Table 6). However, the treatment regimens such as ECT, IST and psychosurgery are no longer an acceptable form of treatment, except in special circumstances. Thus, patients who had a history of one of these three treatments were significantly older and had received neuroleptic treatment for a significantly longer period than those who had not (all $P < 0.01$). That is, these results may reflect only aging.

A number of aspects related to neuroleptic medication have been identified as risk factors for TD (Kane and Smith 1982). In our study, a relatively high correlation was found between the severity of TD and the total years of exposure to neuroleptics (Table 3). However, as described in the Results section, this may also reflect aging. Another significant correlation was observed between daily neuroleptic dosage and the severity of TD (Table 3), although this correlation was quite weak. Despite the fact that exposure to neuroleptics has been

considered to play an essential role in producing TD, it was quite difficult to draw a definitive and consistent relationship between these two items. This may mean that TD occurs only in patients who have a special vulnerability for neuroleptic treatment.

Certain limitations of this study with respect to the epidemiological features of TD remain to be discussed. Initially, since this study was not designed as a case-controlled study, some of the variables do not fit in the comparative analyses. Several significant intercorrelations were identified among the demographic and medical variables (Table 3). The higher prevalence rate for TD in patients with a history of ECT presents a sharp contrast with previous studies (Tepper and Haas 1979). However, as already mentioned, the groups with and without a history of ECT were significantly different in both age and total years of exposure to neuroleptics. On the other hand, patients with a diagnosis of affective psychoses had a lower prevalence and incidence of TD than those with schizophrenia, although this difference did not reach statistical significance (Table 6), in contrast to previous reports (Kane et al. 1986; Barnes 1987). However, this contrast could also result from the disproportion between these two diagnostic groups. Although there was no significant difference in age between the two diagnostic groups, schizophrenic patients received neuroleptic treatment 2.1 times longer ($df = 216$, $P < 0.01$), 3.3-fold higher doses of neuroleptics ($df = 559$, $P < 0.01$) and 2.7-fold higher doses of antiparkinsonian drugs ($df = 288$, $P < 0.01$) than those diagnosed with affective psychoses. Better designed, case-controlled prospective studies would be desirable to evaluate these differences more appropriately.

The relative scarcity of medical information which was obtained prospectively for data analyses must be considered as a second limitation. Although the evaluation of TD was performed prospectively, most of the other medical information was obtained retrospectively at study entry. Patients who developed TD during the study period were receiving significantly lower doses of neuroleptics at study entry than those who did not (Table 4). For this finding, it would be the most reasonable explanation to consider the inclusion of withdrawal dyskinesia in some of the patients with new onset of TD and the latency of obscured TD in those who remained free of TD. However, since no enumeration of the daily dosage of neuroleptics at the time of the second evaluation was performed, no conclusive explanation can be given for this finding.

Another limitation which may exist is the duration of the observation term in this study. A prospective study will prove to be of little worth unless its observation term is long enough. Although the present study has detailed several features regarding epidemiological indexes of TD in Japan, continued follow-up in this ongoing, prospective study should reveal more definitive epidemiological features, including incidence, remission rate and mortality, as well as risk factors for TD.

Acknowledgements. An outline of this paper was presented at the 8th World Congress of Psychiatry, Athens, Greece, 12–19 October 1989. This study was partially supported by the Inogashira Hospital Foundation (Tokyo), the Oumekeiyu Hospital Foundation (Tokyo), NIDA grant DA04264 and NIH grant HL39387 (R.W.R.).

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