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Prevalence and Risk Factors for Tardive Dyskinesia: A Study in an Italian Population of Chronic Schizophrenics

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Summary. The aim of this study was to evaluate tardive dyskinesia (TD) (prevalence and possible risk factors, pharmacological and clinical), in a population of schizophrenic patients after prolonged institutionalization. A total of 148 patients (80 male, 68 female) aged between 28 and 87 years (mean 55, SD 11) diagnosed according to DSM III were included in the study and assessed for the presence and severity of TD using the Abbreviated Rockland Simpson Scale for TD. Of the examined population, 32% were found to be affected by TD. Patients over 55 years had a relative risk of TD that was 2.3 times higher than in subjects under 55 ($P < 0.05$). The most frequent movements were orofacial (60%) and in the extremities (56.4%). No significant relationship between duration of neuroleptic treatments, illness or hospitalization, anticholinergic drugs and TD prevalence was found. Severity was related to age, since there was a positive linear relationship between age and Simpson Scale scores ($r = 0.45$, $P < 0.01$).

Key words: Tardive dyskinesia – Chronic schizophrenia – Prevalence – Risk factors

Introduction

Tardive dyskinesia (TD), the most dramatic and often irreversible side-effect of long-term treatment with neuroleptics (NL), was first described at the end of the 1950s (Schönecker 1957). Epidemiological studies produced since then have shown a high variability in the prevalence of TD. Kane and Smith (1982), reviewing 56 studies performed between 1959 and 1979, found that prevalence varied from 0.5% to 56.4%, with an average value of 20%, but even higher values have been reported in high-risk populations such as the elderly (Casey and Keepers 1988). The extreme variability of TD can be explained by different factors, including population age, sex and diagnostic criteria.

The relationship between NL use and TD has been established, but it is very difficult to identify a clear relationship between TD and pharmacological histories; current literature shows very little evidence that factors like duration of medication or total NL intake are relevant (Kane and Smith 1982; Barnes et al. 1983; Baldessarini et al. 1980). The only variable that seems in all reports to influence the development of TD phenomena is age (Jenner and Marsden 1983). The role of other potential risk factors like anticholinergic drugs and long-acting NL treatment, ECT and continuous treatments is still uncertain.

On the other hand, the difficulty of collecting reliable and complete data not only about patients' psychopharmacological history, but also polypharmacy regimens and high variability in NL prescriptions are additional problems in the study of the influence of certain drugs (NL, anticholinergics) in the development of TD.

The aim of this study was to evaluate TD prevalence and possible risk factors, pharmacological and clinical, in a population of schizophrenic inpatients after prolonged institutionalization (still institutionalized 10 years after the passing of the law that abolished psychiatric hospitals for long-term hospitalizations in Italy).

Patients and Methods

A total of 496 patients resident in a psychiatric hospital in Northern Italy were evaluated for admission to the study. These patients had a history of several hospitalizations before the law of 1978 and refused to leave the hospital or failed to take advantage of community psychiatric services.

In order to be included in the study, patients had to be diagnosed as suffering from schizophrenic disorders according to DSM III and treated with NL. Patients suffering from neurological diseases and alcoholism, or who had been leucotomized or lobotomized were excluded. In all, 148 patients (80 male, 68 female) aged between 28 and 87 years (mean 55, SD 11) with a duration of illness ranging from 9 to 55 years (mean 29.7, SD 9.6) were included in the study. Patients were assessed by two psychiatrists and

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rated for the presence and severity of TD using the Abbreviated Rockland Simpson Scale for TD (Simpson et al. 1979). The assessment was made simultaneously and independently by the two raters and the score was obtained by averaging the two ratings.

Diagnosis of TD was made for a minimum total score of 19, corresponding to one positive item for TD; patients who reached a score of 19 with two doubtful items were assessed again after 3 weeks.

The records of the patients admitted to the study were reviewed for current age, sex, age and diagnosis of the psychiatric onset and duration of illness. For a group of 71 patients (46 males, 25 females) aged between 28 and 80 years (mean 56, SD 11.3) with a duration of illness ranging from 10 to 51 years (30.7, SD 9.8) and whose clinical and pharmacological history was completely documented (total missing records not longer than 6 months), the duration of treatments, the daily dose of NL and anticholinergic drugs, the administration of long-acting NL and ECT were also evaluated.

NL and anticholinergics daily doses were transformed into chlorpromazine and benzotropine equivalents respectively and total intake amounts were calculated.

Statistical analysis included the ANOVA test, Cochran-Mantel-Haenzel tests, regression analysis, and analysis of the level of relative risk.

Results

Of the population examined, 32% were found to be affected by TD. The prevalence of TD was 27% in females and 36% in males; the difference was not statistically significant. In the group of patients with a complete pharmacological history, prevalence was 37%. TD prevalence values were corrected by a rate of spontaneous dyskinesias of 5% (Kane and Smith 1982).

The most frequent movements were orofacial (60%), followed by those in the extremities (56.4%), entire body (20%), and neck and trunk (14.5%). In the orofacial area, the most frequent signs of TD were "bonbon" sign, tremor and choreoathetoid movements of the tongue and movements of the lips, while in the extremities the most frequent movements were in fingers and wrists (Table 1). TD prevalence was higher among subjects over 55 years than among those 55 years or under (39% vs 25%, $P = 0.08$).

Table 1. Frequency of signs of tardive dyskinesia

Sign	Frequency (%)
Periocular area	9
Movements of the lips	18
Chewing movements	18
Bonbon sign	25
Tongue protrusion	9
Tremor and/or choreoathetoid movements of the tongue	20
Axial hyperkinesia	2
Rocking movements	7
Torsion movements	4
Movements of fingers and wrists	40
Movements of ankles and toes	18
Stamping movements	9
Akathisia	16

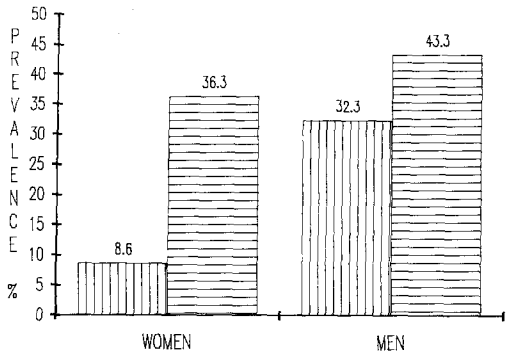

Fig. 1. The prevalence of tardive dyskinesia in males and females under and over 55 years. (▯: Age ≤ 55 years; ▯: age > 55 years)

Table 2. Neuroleptic and anticholinergic treatments of the population

	Min	Max	Mean	SD
Total amount of neuroleptic intake (g CPZ equivalents)	77	9241	3343	1807
Length of neuroleptic exposure (years)	10	33	24	6.5
Total amount of anticholinergic intake (mg benzotropine equivalents)	0	14565	5461	3711
Length of anticholinergic exposure (months)	0	261	96	61

Statistical analysis of the data, stratified by sex and age (with a cut-off at 55 years), showed that TD prevalence was significantly higher among females over 55 years than among those 55 years or under (36.3% vs 8.6%, $P < 0.01$) (Fig. 1). For males, too, the prevalence tended to be higher in patients over 55 (43.3% vs 32.3%), but without reaching statistical significance. Analysis of relative risk showed that patients over 55 years had a relative risk of TD that was 2.3 times higher than in subjects 55 years or under ($P < 0.05$). Taking into consideration only females or males over 55 years the relative risk was respectively 4.5 times ($P = 0.01$) and 1.6 times compared with subjects 55 years or under.

No relationship was found between duration of treatments, illness or hospitalization and TD prevalence. No significant differences were found between affected and non-affected patients, in daily dosage and cumulative intakes of NL and anticholinergic drugs, duration of NL treatment, number of NL, use of long-acting NL, or ECT for the groups of subjects in which the treatments were available. Table 2 shows the main characteristics of drug treatments in all patients.

Patients with a psychiatric onset after the age of 24 years showed a higher prevalence of TD compared with patients with onset at age 24 or below (41.4% vs 24.1%, $P < 0.05$).

Patients with an age of onset of psychiatric illness over 24 had a relative risk for TD that was 2.5 times higher than those with an onset when aged 24 years or under ($P = 0.01$), with not differences between the sexes. With regard to severity, 67% of patients had a score lower

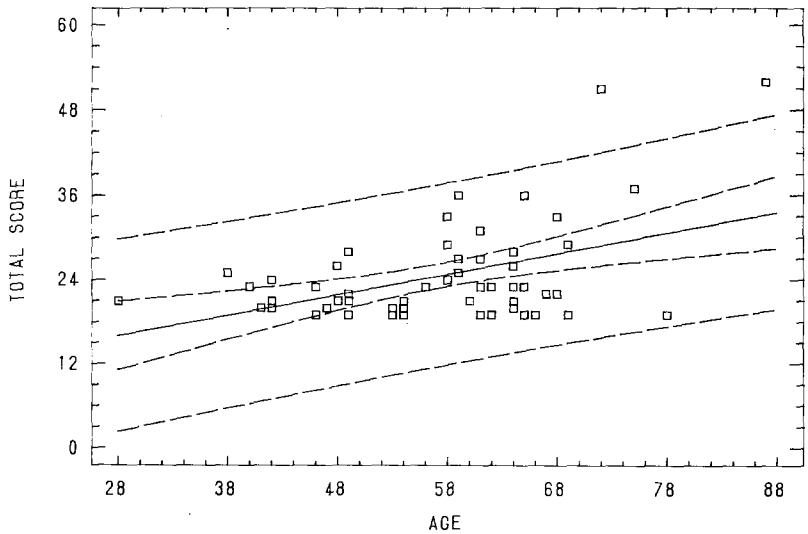

Fig. 2. The linear relationship between age and Rockland Simpson Scale score. Confidence and (outer) predictability limits are also indicated

than 24, while only 15% had a score higher than 30; severity of TD differed significantly in relation to age. In fact, patients over 55 years had mean scores on the Rockland Simpson Scale for TD that were significantly higher than those 55 years or under (26.6, SD 8.4 vs 21.5, SD 2.4, $P = 0.01$). Moreover, there was a positive linear relationship between age and total Rockland Simpson Scale scores ($r = 0.45$, $P < 0.01$) (Fig. 2), which was more evident if only males were considered ($r = 0.6$, $P < 0.01$).

The other variables which were considered did not influence the severity of TD.

Discussion

Among extrapyramidal side-effects induced by NL, TD deserves particular attention because the risk factors are not fully understood and effective treatments are lacking (Altamura 1988).

It has been suggested that TD represents a motor disturbance of schizophrenia (Pfohl and Winokur 1982), since similar movement disorders were also observed by Kraepelin, before the NL era; according to this hypothesis, treatment should have only a "precipitating" effect rather than a causal one. On the other hand, some Authors have emphasized that the repetitive orofacial movements that were described by Kraepelin were clearly different from fragmented and involuntary drug-induced dyskinesias (Marsden et al. 1975). However, evidence of the implication of NL drugs in the development of TD is striking, for at least three reasons. Firstly, although TD is commonly observed in psychotic disorders, it is also described in non-psychotic patients with a wide range of diagnoses, the common factor being previous NL treatment (Gerlach 1979). Secondly, the mean prevalence rate of spontaneous dyskinesias is significantly lower than that of TD (5% vs 20%) (Kane and Smith 1982). Finally, a continuous increase of TD prevalence rates has been reported since the introduction of NL drugs (Kane and Smith 1982).

This study started from the belief that reliable investigations in TD in different cultural and genetic contexts are of interest, since epidemiological data can be influenced by different variables including genetic and/or cultural (i.e. habit of prescriptions) background.

Apart from this consideration, the special features of this study were the long history of institutionalization, the high percentage (36%) of subjects over 60 years, and, finally, diagnostic homogeneity. In fact, data were only obtained from patients diagnosed as schizophrenics without mixing different psychopathological situations.

Moreover, to our knowledge, they are the first available in the international literature on the prevalence of TD in an Italian chronic psychiatric inpatient population. Our findings are mostly in accordance with other literature reports (Kane and Smith 1982).

The high prevalence rate found may be explained by two factors currently considered as determinant for the development of TD. These are firstly age, and secondly the prolonged period of exposure to NL (Casey and Keepers 1988; Kane and Smith 1982). It does not seem likely that a genetic factor can account for this difference. Published data show that the highest prevalence rates are found in the chronically ill in public hospitals (Kane and Smith 1982; Kane et al. 1983) in which these two variables are strongly represented and become additive.

Age is a crucial factor in developing TD: Smith and Baldessarini (1980), in a review which pooled results from 9 studies, showed that TD prevalence rates increased from 10%, in populations under 40 years, to over 50% in patients 60 years of age or above.

The mean age of our population sample was 55, SD 11 with 36.5% of subjects over 60: on this basis the prevalence rate of 32% is fully in agreement with the data in the literature (Casey and Keepers 1988). It is worth mentioning that in this sample TD prevalence and severity proved to be influenced by age but not by duration of treatment, as reported by others (Baldessarini et al. 1980; Kane and Smith 1982; Toenniessen et al. 1985); this would suggest that the effect of age on TD is not

due to a bias of prolonged NL exposure, which probably occurs in elderly patients.

With reference to the severity of TD symptoms, our findings support a strong correlation with age, but not with total dose or type of NL. In elderly subjects, TD symptoms are more severe, and spontaneous remissions seem to be infrequent (Smith and Baldessarini 1980) and this is believed to explain the higher TD prevalence rates occurring in aged populations (Casey and Keepers 1988; Kane and Smith 1982).

Age-related vulnerability to TD after NL medication may be secondary to qualitative changes in receptor sensitivity to NL in the CNS in the elderly or to impairment in drug metabolism occurring with age for different psychotropic drugs, leading to higher brain concentrations of the parent compounds (Altamura 1988; Kane and Smith 1982). In this sample there was no significant difference in the prevalence of TD between the sexes; the higher prevalence reported in females could be an artefact rather than reflecting real biological differences between the sexes.

Concerning the possible pharmacological risk factors, no significant correlation or difference was found in the length, total amount, type or preparation used in NL therapy of patients suffering from TD or not, as has also been reported by others (Casey 1987; Kane and Smith 1982; Baldessarini et al. 1980).

Finally, it is important to point out the lack in our findings of any role of anticholinergic drugs in the prevalence or severity of TD. The use of these drugs is unavoidable in many cases of NL-treated patients (Altamura 1988) and it is essential to exclude a potential risk of increasing the chance of developing TD.

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