RISK FACTORS FOR TARDIVE DYSKINESIA
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Three hundred and fifty three patients who had been on antipsychotics for three months or more were assessed using Simpson Tardive Dyskinesia Rating Scale. 40.2% of these patients, who merited a diagnosis of probable Tardive Dyskinesia (TD) by the Schooler and Kane criteria, were reassessed three months later and 25.5% of the total sample were found to have persistent TD. Age, total antipsychotic dosage and duration of antipsychotic exposure were found to be positively correlated with persistent TD.

INTRODUCTION

A variety of risk factors have been implicated in the aetiology in Tardive Dyskinesia (TD) (Kane & Smith, 1982). However, there are few studies that have utilized a well-defined criteria for diagnosis of TD like the Schooler and Kane criteria (1982) and looked into the putative risk factors in non-western population. We report our findings of such a study on an Indian population.

METHODS

For a period of three months all outpatients attending the psychiatry outpatient clinic who had been on antipsychotics for three months or more were surveyed for the presence of TD. All patients were surveyed by a single rater who was blind to the diagnosis and pharmacotherapeutic status of the patient. They were rated on the Simpson Tardive Dyskinesia Rating Scale (Simpson et al, 1979) which had been standardized in our setting and inter-rater reliability was established. Intraclass correlation coefficient (r) for face, neck and trunk, upper and lower extremities were 0.84, 0.93, 0.71 and 0.44 respectively. All ratings were carried out between 2.00 and 4.00 p.m. Patients who met the diagnosis of "Probable TD" according to the Schooler and Kane criteria became the study group and the patients who did not meet the criteria formed the comparison group. All patients who met the diagnosis of probable TD were resurveyed three months after the initial assessment.

The information on risk factors was collected and analyzed by persons who were blind to the patients’ TD status. The factors examined were age, sex, total antipsychotic, anticholinergic, antidepressant and lithium exposure, prior extrapyramidal syndromes, duration of treatment and diagnosis. Relative risk and 95% confidence intervals were computed. The Chi-square test was used to assess the significance of relative risk. Logistic regression analysis was done using EGRET software.

RESULTS

The total number of patients surveyed were 365. However, 12 patients who received a diagnosis of Probable TD did not come for a follow-up assessment after three months and were dropped from the study; hence, only 353 patients completed the study. The number of patients having TD and the distribution of the types of TD are given in Table 1, and the results of the bivariate analyses are presented in Table 2.

Table 1

| Distribution of type of Tardive Dyskinesia | No. | %  |
|------------------------------------------|-----|----|
| Non-Persistent TD                        |     |    |
| Masked - Probable                        |  7  |  2.0|
| Transient                                | 27  |  7.6|
| Withdrawal                               | 18  |  5.1|
| Persistent TD                             | 90  | 25.5|
| Normal                                   | 211 |  59.8|

Age, total antipsychotic exposure and duration of antipsychotic exposure were significantly associated with TD. When TD was divided into persistent and non-persistent TD and analyzed separately, the above risk factors were seen to be associated with persistent TD only.

The results of logistic regression analysis are presented in Table 3. After controlling for other variables, age and duration of antipsychotic exposure were significantly associated with TD. When TD was divided into Persistent and Non-Persistent TD and analyzed separately the above risk factors were seen to be associated with Persistent TD only.

DISCUSSION

The mean age of our sample was 33.5 years and in our patient population, increasing age was significantly associated with TD. This agrees with findings on Caucasian population literature which
Table 2
Crude Relative Risk and 95% Confidence Interval

|                  | Non-Persistent TD vs Normal | Persistent TD vs Normal | TD vs Normal |
|------------------|-----------------------------|-------------------------|-------------|
|                  | RR  CI                       | RR  CI                  | RR  CI      |
| Age (years)      |                             |                         |             |
| <20              | 1.0 0.3-2.7                 | 1.3 0.7-1.9             | 1.1 0.7-1.9 |
| 21-30            | 1.0                          | 1.0                     | 1.0         |
| 31-40            | 1.2 0.6-2.4                 | 1.4 0.8-2.2             | 1.3 0.9-1.8 |
| 41-50            | 2.0 1.0-4.0                 | 1.8 1.1-3.0             | 1.7 1.1-2.4 |
| >51              | 2.7 1.3-5.7                 | 2.0 1.1-3.7             | 1.9 1.3-2.8 |
| Sex              |                             |                         |             |
| Male             | 1.0                          | 1.0                     | 1.0         |
| Female           | 1.1 0.7-1.7                 | 0.8 0.4-0.9             | 0.8 0.6-1.1 |
| Antipsychotic Exposure |                      |                         |             |
| <1,000           | 1.0                          | 1.0                     | 1.0         |
| 1,000-10,000     | 1.3 0.7-2.2                 | 1.9 1.3-3.4             | 1.6 1.1-2.2 |
| >10,000,000      | 1.3 0.6-3.1                 | 2.5 1.4-4.5             | 1.7 1.1-2.6 |
| Anticholinergic Exposure |                    |                         |             |
| <1,000           | 1.0                          | 1.0                     | 1.0         |
| 1,001-10,000     | 0.9 0.5-1.6                 | 1.4 0.9-2.1             | 1.2 0.9-1.5 |
| >10,000,001      | 1.9 1.0-3.7                 | 2.1 1.3-3.4             | 1.7 1.2-2.4 |
| Antidepressant Exposure |                  |                         |             |
| <1,000           | 1.0                          | 1.0                     | 1.0         |
| 1,001-10,000     | 1.2 0.7-2.2                 | 0.9 0.5-1.4             | 1.0 0.7-1.4 |
| >10,000,001      | 0.7 0.2-2.8                 | 0.8 0.3-1.9             | 0.8 0.4-1.6 |
| Total Lithium Exposure |                  |                         |             |
| <1,000           | 1.0                          | 1.0                     | 1.0         |
| 1,000-10,000     | 1.0 0.6-2.1                 | 0.7 0.3-1.3             | 0.8 0.5-1.3 |
| >10,000,001      | 1.0 0.3-3.6                 | 1.6 0.9-2.8             | 1.3 0.8-2.1 |
| Prior EPS        |                             |                         |             |
| No               | 1.0                          | 1.0                     | 1.0         |
| Yes              | 1.2 0.5-2.9                 | 1.9 0.9-4.0             | 1.6 0.9-2.9 |
| Duration (months)|                             |                         |             |
| 0-6              | 1.0                          | 1.0                     |             |
| 7-12             | 0.5 0.2-1.5                 | 1.8 0.7-4.2             | 1.1 0.5-1.8 |
| 13-24            | 1.2 0.6-2.5                 | 1.6 1.1-5.8             | 1.6 0.9-2.6 |
| 24-60            | 1.8 0.9-3.7                 | 4.7 2.2-9.9             | 2.4 1.5-3.7 |
| 61               | 1.4 0.7-3.0                 | 2.0 0.9-1.1             | 2.1 1.3-3.4 |
| Diagnosis        |                             |                         |             |
| Schizophrenia    | 1.0                          | 1.0                     | 1.0         |
| Affective Disorder | 0.8 0.1-1.3                 | 0.7 0.5-1.0             | 0.8 0.6-1.0 |
| Paranoid state   | 1.2 0.5-2.6                 | 1.1 0.6-1.8             | 1.0 0.7-1.6 |

OR = Odds ratio; CI = 95% Confidence Interval
* p<.05; ** p<.01; *** p<.001

Table 3
Results of Logistic Regression Analysis

| Variables                | Persistent TD vs Normal | TD vs Normal |
|--------------------------|-------------------------|-------------|
|                          | OR  CI                  | OR  CI      |
| Age (years)              |                         |             |
| <20                      | 2.6 1.0-7.0             | 1.7 0.7-4.0 |
| 21-30                    | 1.0                     |             |
| 31-40                    | 1.5 0.7-3.2             | 1.5 0.8-2.8 |
| 41-50                    | 2.4 1.0-5.8             | 2.6 1.3-5.4 |
| >51                      | 3.5 1.1-10.9            | 3.7 1.4-9.8 |
| Sex                      |                         |             |
| Male                     | 1.0                     |             |
| Female                   | 0.5 0.3                 | 1.0         |
| Antipsychotic Exposure   |                         |             |
| <1,000                   | 1.0                     |             |
| 1,001-10,000             | 0.6 0.1                 | 1.0         |
| >10,000,001              | 0.6 0.1                 | 0.2 0.2-2.1 |
| Anticholinergic Exposure |                         |             |
| <1,000                   | 1.0                     |             |
| 1,001-10,000             | 0.6 0.3                 | 1.0         |
| >10,000,001              | 0.6 0.3                 | 0.2 0.3-1.3 |
| Antidepressant Exposure  |                         |             |
| <1,000                   | 1.0                     |             |
| 1,001-10,000             | 0.6 0.2                 | 1.0         |
| >10,000,001              | 0.6 0.2                 | 0.0 0.0-0.8 |
| Total Lithium Exposure   |                         |             |
| <1,000                   | 1.0                     |             |
| 1,001-10,000             | 0.5 0.2                 | 1.7         |
| >10,000,001              | 0.5 0.2                 | 0.3 0.3-1.6 |
| Prior EPS                |                         |             |
| No                       | 1.0                     |             |
| Yes                      | 2.4 0.9                 | 1.9         |
| Duration (months)        |                         |             |
| 0-6                      | 1.0                     |             |
| 7-12                     | 2.6 0.8                 | 7.9         |
| 13-24                    | 4.1 1.2                 | 14.0        |
| 24-60                    | 14.5 3.8                | 56.5        |
| 61 of over               | 10.2 0.2                | 45.8        |
| Diagnosis                |                         |             |
| Schizophrenia            | 1.0                     |             |
| Affective Disorder       | 1.2 0.5                 | 2.7         |
| Paranoid state           | 2.0 0.7                 | 5.7         |

OR = Odds ratio; CI = 95% Confidence Interval
* p<.05; ** p<.01; *** p<.001
suggest that age is almost linearly related to prevalence of TD from 20 to 40 years (Chouinard et al., 1986).

The mean duration of exposure to antipsychotic medications was 33.4 months in our patient population. The prevalence of TD was strongly correlated with the duration of exposure to antipsychotic and this also agrees with studies done on Caucasian population (Kane et al., 1986).

An interesting finding emerged with regard to total antipsychotic exposure. Most studies which show a positive association between total antipsychotic exposure and TD, involved samples with relatively low cumulative drug exposure. As Kane and Smith (1982) point out, perhaps for those who are vulnerable to the development of TD, a dose response relationship occurs at relatively low cumulative doses, whereas for those without this underlying vulnerability increasing doses beyond this range may not lead to substantial increase in the risk of TD. In our study, the mean cumulative dose was 362,985 mgms chlorpromazine equivalent, which is on the lower side of the usual cumulative antipsychotic dose reported in studies on TD (Kane & Smith, 1982) and this was found to be significantly correlated with persistent TD in the bivariate analysis. However, on multivariate analysis, this correlation did not reach significant level. This may mean that in our population, the 'threshold' of exposure to antipsychotic exposure for development of TD is below this cumulative dose. Perhaps further studies on lower cumulative dose may establish a positive correlation.

In our patient population, the sex of the patient was not found to be significantly associated with development of TD. Most recent reviews indicate that the magnitude of sex difference in TD (i.e., females having a higher prevalence of TD) increased with increasing age (Chouinard et al., 1986). Our sample was relatively young (mean age 33.53) and this could be the reason for the insignificant difference between the sexes. Diagnosis, exposure to lithium carbonate and tricyclic antidepressants were not correlated with the prevalence of TD. Though there was a correlation with the use of anticholinergics on bivariate analysis, this disappeared on multivariate analysis. Since longer duration of treatment with antipsychotics invariably results in higher cumulative dose of anticholinergics, this finding suggests that it may not be the use of anticholinergics per se which is important in the genesis of TD, but only the duration of exposure to antipsychotics.

One of the major limitations of the study was that there was a single rater for all the TD assessments; but the good inter-rater reliability which was established at the beginning of the study and the fact that the TD rater was blind to the patients pharmacotherapeutic status and those who collected information on possible risk factors were blind to the patient’s TD status decreased the chances of observer bias. Another limitation was that although the information regarding the past medication was gathered from the patient’s hospital charts in most cases, in a few, the information had to be based on the reports from patients and their relatives. This could have been erroneous, even though a great effort was made to be as accurate as possible.

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