Clinical and familial correlates of tardive dyskinesia in India and Israel

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ABSTRACT

Background: Antipsychotic drugs are widely used for the treatment of psychosis, especially schizophrenia. Their long-term use can result at times in serious side-effects such as Tardive Dyskinesia (TD). Since over 80% of schizophrenia sufferers (lifetime prevalence 1%) receive long-term antipsychotic drug treatment, the extent of the problem is potentially large. Increasing age is the most consistently demonstrated risk factor for TD.

Aims: To assess effect of different clinical factors and demographic variables in India and Israel and sib pair concordance of Tardive Dyskinesia (TD) in India.

Settings and Design: The study was conducted simultaneously among Indian and Israeli subjects: ascertainment was family-based in India and hospital-based in Israel.

Methods and Material: In India the instruments used were: Diagnostic Interview for Genetic Studies (DIGS), Positive and Negative Syndrome Scale (PANSS), Abnormal Involuntary Movement Scale (AIMS), and Simpson Angus Scale (SAS). The last three instruments were also used in Israel.

Statistical Analysis: Regression analysis and Pearson's correlation.

Results and Conclusions: TD symptoms were present in 40.4% of 151 Israeli subjects and 28.7% of 334 Indian subjects. While age at onset and total scores on PANSS were significant predictors of TD in both the samples, lower scores on the Global Assessment of Functioning Scale (GAF), diagnostic sub-group and male gender were significant predictors among Indians. There was no concordance of TD symptoms among 33 affected sib-pairs from India.

KEY WORDS: Tardive dyskinesia, schizophrenia, genetic, familial

Tardive dyskinesia (TD), with a prevalence of 20% is one of the most serious adverse effects of treatment with Dopamine antagonists (DA).[1] TD poses significant public health problems and increased morbidity due to difficulties in mobility, speech, eating and swallowing.

Increasing age (estimated risk among older patients—60%)[2] is the most consistently demonstrated risk factor for TD. Other factors, less consistently documented, include duration and intensity of prior antipsychotic drug exposure, female gender, negative symptoms and a diagnosis of affective disorder.[3,4,5,6,7,8,9,10]

The prevalence of TD may also vary across ethnic groups: 40% of Chinese subjects and 29% of Malay subjects had TD in a recent survey.[11] Among the very few studies available on the prevalence of TD among Indian patients, Datta et al[2] estimated its prevalence (persisting over three months) at 25.5% in a sample of 353 patients. Age, total antipsychotic dosage and duration of antipsychotic treatment correlated positively with per-

sistent TD.

The variable prevalence of TD across different ethnic groups is compatible with a genetic or an environmental aetiology for TD, in addition to the risk conferred by treatment. Indeed, earlier reports suggested intra-familial correlations.[12] Significant concordance for TD among pairs of affected siblings exposed to antipsychotics was reported by Hotamisilgil et al.[13] Waddington and Yousseff[14] reported a family in which nine siblings were affected with psychiatric disorders; five of whom were diagnosed with schizophrenia and all of them manifested TD. McCreadie et al[15] concluded in their study on Indian subjects that Dyskinesia but not parkinsonism is more common in siblings of people with schizophrenia who have the corresponding movement disorder. In a retrospective comparison of a sample suffering from chronic schizophrenia, those manifesting TD showed a significantly higher rate of family history of psychiatric disorder.[16]

In the present study we investigated the role of clinical (both groups) and familial (Indians only) factors associated with the expression of TD among Indian and Israeli patients. Similar analyses were conducted simultaneously in these two samples, in order to evaluate consistencies among the putative risk factors. We reasoned that risk factors identifiable in both samples would be more credible, though the unique features of these two ethnic groups could also yield differences.

Materials and Methods

All probands from participating centres were screened for TD by Research Diagnostic Criteria-Tardive Dyskinesia (RDC-TD).[17] Probands who received a rating of mild dyskinesia in two or more body areas, or of moderate or severe dyskinesia in any body part on the basis of the (Abnormal Involuntary Movement Scale) AIMS, were categorized as having TD according to RDC-TD. Probands were assessed only once. Therefore, the diagnosis of TD in our sample corresponded to the category termed 'cross-sectional TD'.[18] The ascertainment was familial in India and hospital-based in Israel in this study lasting for two years. The Israeli sample consisted of schizophrenia subjects alone. The probands in the Indian sample were either single probands or affected sib pairs. For single probands, both parents needed to be alive and willing to participate in the study to qualify them for inclusion.

In Israel, the inclusion criteria included: (1) diagnosis of schizophrenia according to DSM-IV[17] (2) age 18-65 years; (3) male or female; (4) lifetime duration of exposure to antipsychotic drugs of at least three months; (5) Jewish (6) stable dose of antipsychotic and anticholinergic medication for at least three months prior to evaluation; (7) willingness to participate in the study and to give written informed consent. Patients with a lifetime history of alcohol/substance dependence or of abuse within the last five years, active or past medical or neurological illness that might confound study assessments or of mixed or uncertain ethnic origin were excluded. A total of 60 patients who fulfilled Research Diagnostic Criteria –Tardive Dyskinesia (RDC-TD) [17] and 91 patients without TD were recruited.

In India, parents were also interviewed to determine both family history as well as proband's symptoms. The primary recruitment site was a publicly funded tertiary care hospital providing inpatient and outpatient care. In addition, all major hospitals and psychiatric rehabilitation facilities in the city were approached regularly. Though most patients at such facilities resided in the metropolitan limits, approximately one-third were drawn from rural areas surrounding the metropolis. Other inclusion criteria were: diagnosis of schizophrenia or schizoaffective disorder according to the Diagnostic Statistical Manual (DSM-IV), age less than 60 years; male or female, lifetime duration of exposure to antipsychotic drugs of at least three months, and able and willing to give written informed consent. Diagnostic Interview for Genetic Studies (DIGS) includes comprehensive sections on depression, mania and psychosis and requires longitudinal history of the total illness period. The parents of the probands accompanied them in India and history of illness was obtained from both. The facts obtained were reliable, and diagnosis was determined after extensive review and re-interview if necessary. A total of 334 probands participated. It was not possible to determine the exact amount or dosage of antipsychotic drugs for the Indian patients as dosage changed with the severity and duration of illness, and treatment records were usually unavailable. While names of medicines prescribed were easy to recall for the proband and parents, dosage could not be recalled. Duration of exposure to antipsychotic medications for at least three months was ascertained and was considered essential for participation.

The following scales were used in the study

(i) **Diagnostic Interview for Genetic Studies (DIGS)**: Developed by Nurnburger et al[19] (http://www-grb.nimh.nih.gov/gi.html) and translated into Hindi by Deshpande et al[20] the DIGS is a comprehensive semi-structured interview schedule, also including extensive clinical and demographic information. Diagnosis is established using DSM IV. Probands and parents were interviewed together. Medical records were obtained to the extent possible so as to aid diagnosis, and obtain history of treatment.

(ii) **Abnormal Involuntary Movement Scale (AIMS)[21]:** This is the principal scale for rating the severity of dyskinetic movements. Orofacial, neck-trunk and distal (limb) movements are rated separately. Orofacial TD is rated for muscles of facial expression, lips and perioral area, jaw movements and tongue movements. Extremity movements are rated for upper and lower limb movements. Trunk movements are rated for neck, shoulders and hip movements. An AIMS Total Score (orofacial, neck-trunk, limbs) reflects the overall severity of dyskinetic movements. To establish the diagnosis of TD, Research Diagnostic Criteria (a total of two mild or at least one moderate or higher rating in any of the categories) were followed.

(iii) **Simpson Angus Scale (SAS)[22]:** This is an internationally accepted scale for rating dystonia in different muscles of the body. The total of SAS score suggested the severity of TD in the subject.

(iv) **Positive and Negative Syndrome Scale (PANSS)[23]:** This is an internationally standardized scale for comprehensive assessment of psychopathology and symptom dimensions. This scale derives from the Brief Psychiatric Rating Scale and includes positive symptoms, negative symptoms and general psychopathology subscales. PANSS provides detailed operationalized rating criteria including definitions for 30 symptoms at seven rating levels. It includes seven items for positive symptoms, seven items for negative symptoms and a general psychopathology scale.

Means and standard deviations were calculated for demographic and clinical variables and measures of TD. Pearson's correlation was carried out to determine the relationship between the two TD scales used. Regression analysis was also performed utilizing the Statistical Package for Social Sciences (SPSS, version 11.5 for Windows): linear for continuous variables and binary logistic for categorical variables.

All participants and/or guardians provided written informed consent, as approved by the Ethics Committees at the different participating hospitals and universities; after which the proband was interviewed using DIGS. Diagnosis was established based on DSM IV criteria. TD was assessed using AIMS and SAS. Parents were interviewed and detailed family history data obtained by means of the Family Interview for Genetic Studies (FIGS). In Israel interview and assessment was completed as per the instruments listed above with the exception of DIGS and FIGS. The study was conducted prospectively, over a two-year period.

Results

The mean age of the total Indian sample was 32.4±13.7 years. The mean age of those with TD was 34.77±12.6 (Table 1). Males constituted 45.8% of the TD positive sample. On AIMS, 96 cases [28.7%; 59 females (61.5%)] out of a total of 334 Indian probands had TD. Simpson Angus Scale and AIMS showed significant correlation in the Indian sample. Mean of AIMS total score was 2.29±3.25 (6.29±3.48 for TD positive cases) while mean orofacial score was 1.56±2.28 (4.02±2.77 for TD positive), mean extremity score 0.53±1.29 (1.72± 1.90 for TD positive) and mean trunk score 0.09±0.29 (0.32±0.47 for TD positive). Mean Simpson Angus Score was 4.55±6.31 (12.55±6.36 for TD positive cases) among Indian cases.

Among 96 Indian patients with TD, 39.6% had received only typical antipsychotic drugs, 47.9% had only received atypical/newer antipsychotics (including Clozapine, Risperidone, and Olanzapine) and 12.5% had received both types of drugs during the past three months. There were no significant differences between "TD present" and "TD absent" cases with respect to type of antipsychotic drug exposure.

Regression analyses were performed separately using the following dependent variables: AIMS scores, total SAS scores and presence or absence of TD (based on the AIMS). The covariates used for the Indian sample were gender, scores for positive symptoms, negative symptoms and general psychopathology, as well as marital status, education, age at onset, pattern of symptoms, longitudinal course, pattern of severity, global assessment of functioning at worst point during current episode and during past month, and diagnosis.

In the Indian sample, on linear regression analysis, male gender ($p=0.017$), early age at onset ($p<0.001$), low education ($p<0.001$) and low GAF scores at "worst point during current episode" ($p=0.007$) were significant predictors of total AIMS score. Following logistic regression analysis for TD yes/no using AIMS as dependent variable, earlier age at onset ($p=0.003$), lower educational attainment ($p<0.001$), low GAF scores (Global Assessment of Functioning at worst point during current episode) ($p=0.047$) and schizoaffective disorder ($p=0.002$) were significantly associated with the presence of TD in this sample. When the proband was not actively ill (73 cases) at the time of assessment, GAF score had to be marked '0' (DIGS manual). When logistic regression analysis was carried out after omitting these cases, low GAF score was not associated with TD ($p=0.139$). Following linear regression analysis with SAS as the outcome, the only significant variables were lower positive symptom score ($p=0.014$) and higher negative symptom score on PANSS ($p=0.006$) (Table 2).

There were 33 sib pairs in the Indian sample. Only one sib pair was concordant for TD, while neither sib among the other 32 sib pairs had TD. Thus, meaningful sibling correlations could not be tested.

The mean age of the Israeli sample was 47.6 ±11.09 yrs. The mean age of those with TD was 52.57±13.66. Males and females were equally distributed among those with TD. Using the AIMS scale, 40.4% of the total 151 Israeli probands had TD. Of the 79 males recruited, 36.7% and of 72 females, 43% were affected with TD. There were significant correlations between the SAS and AIMS Total in this sample also.

In the Israeli sample, mean AIMS total score was 5.08±6.18 (10.85±6.15 for TD positive cases) and 1.56±2.28. The mean orofacial score was 3.22±3.98 (6.9±3.97 for TD positive), mean extremity score was 1.38±2.01 (2.9±2.34 for TD positive) and mean trunk score was 0.48±0.95 (1.0±1.25 for TD positive). Mean Simpson Angus Score (SAS) was 8.06±7.78 (12.02±10.19 for TD positive cases).

In the Israeli sample, none of the patients were receiving atypical antipsychotic drugs at the time of the study. All had received typical antipsychotic drugs.

Variables considered for regression analysis in the Israeli sample were sex, age at onset and PANSS total score. Age at onset ($p< 0.001$ and $p=0.002$) and PANSS total score ($p< 0.001$)

Table 1: Demographic and TD Variables in India and Israel

Variable	India (N=334)		Israel (N=151)	
	TD Present	TD Absent	TD Present	TD Absent
Mean Age in Years and Standard Deviation	34.77 ± 12.6	31.49 ± 10.29	52.57 ± 13.66	44.35 ± 12.78
Mean Age at Onset in Years	24.77 ± 8.87	22.21 ± 6.93	28.25 ± 10.94	22.56 ± 7.94
Mean PANSS Total Score	63.06 ± 19.05	57.76 ± 18.59	98.15 ± 27.56	85.16 ± 33.3
Mean Simpson Angus Total Score	12.55 ± 6.36	1.33 ± 1.88	12.02 ± 10.19	5.45 ± 3.92
Mean AIMS Total Score	6.29 ± 3.48	0.69 ± 0.99	10.85 ± 6.15	1.27 ± 1.43
Mean Orofacial Total Score (AIMS subscale)	4.02 ± 2.77	0.57 ± 0.90	6.9 ± 3.97	0.80 ± 1.07
Mean Extremity Total Score (AIMS subscale)	1.72 ± 1.90	0.05 ± 0.30	2.9 ± 2.34	0.07 ± 0.71
Mean Trunk (AIMS subscale) Total Score	0.32 ± 0.47	0.00 ± 0.00	1.0 ± 1.25	0.09 ± 0.33

TD: Tardive Dyskinesia; AIMS: Abnormal Involuntary Movement Scale; PANSS: Positive and Negative Symptoms Scale

Table 2: Regression Analysis of Indian samples

TD Variable (Dependent)	TD Variable (Independent)	Beta	*P* Value	Confidence Interval for Beta
	Linear Regression Analysis			
AIMS Total Score	Age at onset	0.272	<0.001	(0.067, 0.169)
	Sex	0.154	0.017	(0.233, 1.686)
	Education	-0.310	<0.001	(-0.318, -0.142)
	GAS 1	-0.163	0.007	(-0.90, -0.014)
Simpson Angus Total Score	Negative Symptoms Score (PANSS)	0.218	0.006	(0.030, 0.176)
	Positive Symptoms Score (PANSS)	-0.192	0.014	(-0.202, -0.023)
	Logistic Regression Analysis			
	TD Variable (Independent)	Beta	*P* Value	Confidence Interval Odds Ratio
AIMS (Yes/No)	Age at onset	-0.065	0.003	(0.898, 0.978)
	Education	0.157	<0.001	(1.086, 1.262)
	GAS 1	0.036	0.047	(1.000, 1.075)
	Diagnosis	-0.651	0.002	(0.345, 0.787)

GAS 1: Global Assessment of Symptoms at Worst Point During Current Episode; **AIMS:** Abnormal Involuntary Movement Scale; **PANSS:** Positive and Negative Symptoms Scale

were significant predictors of AIMS Total score and Simpson Angus Total score (using linear regression). Using TD present or absent on AIMS as dependent variable, on logistic regression age at onset ($p<0.001$) and PANSS scores ($p=0.005$) were found to be significant (Table 3).

Discussion

The Indian and Israeli samples were studied in two different settings: inpatient, long-term care settings in the Israeli group, and outpatient or short-term care facilities in the Indian group. The Indian sample was family-based and required participation by both parents due to the requirements of the genetic research protocol (and resulted in younger age at interview). Single Israeli probands with TD were recruited. Hence no attempt at comparison was made for the two samples. We elected to conduct multi-variate analyses separately to detect factors that were correlated with TD in both differing samples. Age at onset and total PANSS scores were significant predictors among others in both the samples analysed separately.

The Israeli subjects were more severely ill than the Indian subjects, as indicated by the higher PANSS scores. This may have contributed to their higher TD scores. In support, considering both national groups together, the PANSS total score of those with TD was significantly more than those without ($t=4.262$, $p<0.001$). Higher doses of antipsychotics might have been required to control symptoms leading to TD. It has been suggested that variation in the prevalence of TD is more likely to be determined by differences in the duration of exposure and dose levels of antipsychotic drugs.[10] TD vulnerability may also be a constitutional feature of a more severe schizophrenia phenotype that requires typical antipsychotic drug exposure for its expression. This constellation may also include unsatisfactory therapeutic response and greater severity of negative symptoms.[24] TD has been observed among non-medicated individuals with schizophrenia, suggesting a more intrinsic biological process independent of antipsychotic medication.[25] Illness severity is also associated with increased cognitive dysfunction, hence the correlation between TD and progressive cognitive dysfunction[26] may indicate a primary association between TD and severity.

The expression of TD i.e. the type of muscle groups involved, hence the type of symptoms expressed clinically differed between the two groups. This suggests that while universal genetic mechanisms operated in schizophrenia as well as TD, specific expression of particular disorders may differ among different ethnic groups and may be mediated by treatment factors.

Other factors were associated with TD in the Indian sample.

Table 3: Regression Analysis of Israeli samples

TD Variable(Dependent)	TD Variable (Independent)	Beta	*P* Value	Confidence Interval for Beta
	Linear Regression Analysis on AIMS and SAS Scores			
AIMS Total Score	Age at onset	0.370	<0.001	(0.149, 0.326)
	PANSS	0.391	<0.001	(0.049, 0.104)
Simpson Angus Total Score	Age at onset	0.228	0.002	(0.071, 0.298)
	PANSS Total	0.464	<0.001	(0.080, 0.149)
	Logistic Regression Analysis on AIMS			
TD Variable(Dependent) AIMS (Yes/No)	TD Variable (Independent)	Beta	*P* Value	Confidence Interval for Odds Ratio
	Age at onset	-0.071	<0.001	(0.895, 0.149)
	PANSS Total	-0.016	0.005	(0.973, 0.995)

TD: Tardive Dyskinesia; **AIMS:** Abnormal Involuntary Movement Scale; **SAS:** Simpson Angus Scale; **PANSS:** Positive and Negative Symptoms Scale; **CI:** Confidence Interval

These included positive and negative symptoms scores of PANSS which correlated with SAS total score, lower global assessment score at worst point of current episode (suggesting higher severity of illness), and early age at onset (AIMS total and TD present or absent on AIMS). These results are consistent with published reports.[7,8,9.]

Atypical antipsychotic drugs are said to cause extra-pyramidal symptoms less often (only one percent) and are also reported to be associated with less severe TD than older, typical antipsychotic drugs (five percent).[27] Jeste et al[28] concluded that the atypical anti-psychotic drug Risperidone was significantly less likely to result in TD than the conventional neuroleptic Haloperidol in a high-risk group of older patients, at least over a nine-month period. Allan et al[29] investigated the relationship between measures of extra-pyramidal and negative symptoms among patients with schizophrenia treated with Haloperidol or Olanzapine: extra-pyramidal symptoms and PANSS negative score were detected in the Haloperidol group only. The prevalence of dyskinesia and parkinsonism was similar in all the groups, possibly related to the age at onset of illness.[30]

Indian subjects with a schizoaffective disorder had a significantly higher prevalence of TD than those with schizophrenia: 26% of 266 schizophrenic subjects and 40% of 68 schizoaffective subjects had TD. In contrast, Schulze et al[31] investigated 174 patients suffering from schizophrenia with affective symptomatology and reported that neither mania nor depression was significantly correlated with TD.

Among a large sample of affected siblings, Ismail et al[32] did not find any co-occurrence of TD. Familial occurrence of TD has been hypothesized to confer risk to the development of TD among index cases. Muller et al[33] reported a trend for TD among the affected relatives to be associated with the TD status of the index-subject with a diagnosis of schizophrenia or schizoaffective disorder; this finding was unrelated to age or doses of neuroleptic medication. However, no association between a family history of schizophrenia or schizoaffective disorder and presence of TD was detected in the Indian sample. Thus, a family history of TD might represent a risk factor for TD; in contrast a family history of schizophrenia may not.

A major limitation of this study is the differing nature of the two samples due to which direct comparisons cannot be made. Strict measures were taken to ensure the reliability of diagnosis and evaluation in the two groups. Medical records of subjects in the Indian sample were usually not available. Hence it was difficult to record exact dose of drugs taken by the subject in the course of illness (minimum duration of drug intake was ensured). Nevertheless, the present study suggests that age and severity of illness are important risk factors for TD.

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Expert's Comments

Use of antipsychotics and tardive dyskinesia

The advent of second generation antipsychotics with their claim of being less lethal in producing tardive dyskinesia (TD) and other movement disorders has burgeoned the interest in TD research. Biological correlates of TD, its nature and response to medication have all been investigated. A series of studies on TD in untreated subjects has also been reported in recent years. The relationship between treatment and TD is not just linear, but influenced by multiple and interrelated factors such as age, duration of illness etc. Age in particular has been addressed using samples of young, middle aged and elderly persons.

Another interesting contribution to the field of TD research is this paper[1] reporting findings of two almost similar works carried out in India and Israel. Nearly 40% of Israeli subjects and 28.7% of Indians had TD. What is of interest in the Indian sample is the fairly high use of atypical antipsychotics compared to the Israel sample. Yet, no differences in TD were observed between those on conventional and atypical antipsychotics. Maybe a longer period of follow-up is required to substantiate this finding. Schizoaffective subjects seemed to have more TD. One wonders whether these people were on higher doses of medication.

While the authors have rightly pointed out the difficulties in comparing the two samples, it is obvious that the Israeli group is sicker, with more TD, older and only on typical antipsychotics. The mean drug dosages of the samples would have been an interesting addition.

This seems to be the right time to embark on more TD research given the scenario that with lesser use of typical antipsychotics, we may see less of TD and other movement disorders. It is also the right time to longitudinally assess the appearance of TD in cohorts only on atypicals.

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References

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