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Tardive Dyskinesia and Dementia

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SUMMARY Seventeen schizophrenic patients with tardive dyskinesia (TD) and 33 schizophrenics without tardive dyskinesia were examined by psychological tests of intellectual function and EMI scans were performed. The group as a whole were found to be demented and 31 out of 45 had abnormalities on the scan. On a learning test the tardive dyskinesia group did significantly worse and using a measured parameter of the scan (the Ventricular Index) the tardive dyskinesia group had more abnormality. It is suggested that the higher incidence of pathology in the tardive dyskinesia group may be related to chronic neuroleptic toxicity.

It has been suggested by Johnstone *et al* (1978) that there may be a group of schizophrenic patients who develop intellectual deterioration with objective (EMI Scan) evidence of cerebral degeneration. It could be, as suggested by Jellinck (1976), that conditions in mental hospitals may be such as to produce brain disease and dementia. A second possibility is that the dementia is due to long-continued administration of neuroleptic drugs. One side effect of neuroleptic administration is tardive dyskinesia, which is thought to be due to the development of dopamine receptor supersensitivity. Such supersensitivity may be a pharmacological response to the dopaminergic blockade but could also be due to a degeneration of dopaminergic neurones as seen in Parkinson's disease, since there is evidence of post-mortem degenerative change in the substantia nigra of patients who have been treated with neuroleptic drugs (Christenson *et al*, 1970). A degeneration could also be taking place in systems post-synaptic to the dopaminergic system such as GABA-ergic or cholinergic neurones.

The hypothesis for this study was that patients with tardive dyskinesia would show a greater degree of dementia than those without, since tardive dyskinesia could be a sign of a more generalized neurotoxic process. Chronic schizophrenic patients were therefore tested psycho-

logically to determine the degree of dementia and the EMI Scan was used for evidence of cerebral degeneration.

Methods

The study was performed on 50 long-stay patients who had a case note diagnosis of schizophrenia and who fulfilled the criteria of Feighner *et al* (1972). Of these, 17 patients had evidence of tardive dyskinesia. Patients were seen at least three times by the examining psychiatrist and nursing observation was taken into account before a judgement was made on the presence or absence of the syndrome. The two groups, i.e. those with and those without tardive dyskinesia, did not differ with respect to age (patients over the age of 60 were excluded), social class, duration of hospitalization, duration of treatment and the sex ratio was not significantly different (Table I).

Psychological tests consisted of the clinical tests of the sensorium (Withers and Hinton, 1971) and in 39 unselected cases (14TD, 25 no-TD), the Inglis (1959) paired associate learning test.

An EMI scan was performed on all the patients and these were reported on a measured 'blind'. Three were found to have evidence of frontal leucotomy and were excluded from the EMI scan data. The degree of ventricular en-

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largement and cerebral atrophy were each graded as normal, mild, moderate and moderately severe and scored as 0, 1, 2 or 3 respectively, so that mild atrophy and mild ventricular enlargement on the scan scored 2 and at the extreme end, moderately severe enlargement and moderately severe atrophy scored 6. The scans were measured for the Huckman number, ventricular index and cella media index as described by Meese *et al* (1976). In some patients the quality of the scan precluded measurement of the various indices or accurate comment from the neuro-radiologist. Drugs currently prescribed to these patients were compared.

Results

Psychological tests

(a) Clinical test of the sensorium (Withers and Hinton, 1971). When compared with previously reported non-schizophrenic controls (Johnstone *et al*, 1978) both the group with and the group without tardive dyskinesia were significantly impaired ($P < .001$) although not as severely as the schizophrenic patients described by those authors. However, in our study both the duration of hospitalization (14.6 years cf. 31.8 years) and the mean age (48.6 years cf. 57.7 years) were lower than in the study of Johnstone *et al*. Only two of the subjects in the present study were disorientated for age (Crow and Mitchell, 1975). No difference was detected in test performance between the two groups in either the subtests or the global rating (Table II).

The results of the global rating scale for the group correlated significantly with age ($r = -.52$, $P < .001$). There was also a significant relationship between the global score and the duration of treatment ($r = -.38$, $P < .01$). However, when the effect of age on this test was partialled out, the true correlation between the duration of treatment and the test then achieved only borderline significance ($r = -.28$, $P = .05$).

(b) The Paired-Associate Learning Test (Inglis, 1959). The group with tardive dyskinesia performed significantly worse than the group without tardive dyskinesia (Table II). Taking the score of 24 as the cut-off point, which is outside the range of the original control series (Inglis, 1959), then of the 14 schizophrenics with tardive dyskinesia, 8 had scores above 24 and of the 25 schizophrenics without tardive dyskinesia, only 3 had scores above 24. This was significant ($P < .005$) by Fisher's exact probability test. There was no significant correlation between the test score and the age of the patient. The differences between the groups cannot be related to the sex ratio which is not significantly different and the PALT scores were not significantly related to sex ($t = 0.13$).

EMI scans

There was a great deal of pathology observed by the neuroradiologist in the EMI scans. Of the total group, 31 out of 45 were rated as abnormal on one or more parameters. When measured the EMI scans fell into the pathological range on the Ventricular Index (TD group) and the cella

TABLE I
Characteristics of 2 groups of patients

	Tardive dyskinesia		No tardive dyskinesia	
	7 male	10 female	19 male	14 female
Sex				
Age	Mean 49.2	SD 5.2	Mean 48.1	SD 6.5
Duration of stay	14.6	6.6	14.6	5.4
Duration of treatment	12.7	6.0	12.4	4.5
Social class	4.25	0.77	4.26	0.63

No significant difference between groups

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media index (Table III). When scored in terms of severity of cortical atrophy and increased ventricular size, no difference emerged between the patients with and without tardive dyskinesia (Table III). There was no difference between the Huckman number and the cella media index between the groups but there were significantly more patients in the tardive dyskinesia group with a pathological rating on the ventricular index (9 out of 10 pathological) when compared with the group without tardive dyskinesia (14 out of 26 pathological) $P < .05$ (Fisher's exact probability one tail test). The Huckman number was the only parameter that correlated with age ($r = -.32, P < .05$).

Of the psychological tests there were no significant correlations between the EMI scores and other parameters. There was a significant correlation between the PALT and the 'scored' EMI scan of the neuroradiologist ($r = .36, n = 35, P < .05$). This correlation held only for the without tardive dyskinesia group ($r = .52, n = 22, P < .05$), and not the group with tardive dyskinesia. There did not appear to be a difference between the dose of oral medication between the groups, but the dose of depot preparation, fluphenazine decanoate, was significantly higher in the tardive dyskinesia group who had weekly doses 28.9 ± 20.6 ($n = 14$) whilst the non-tardive dyskinesia group had an average of 17.5 ± 9.5 ($n = 20$). This was significant using the t-test, ($P < .05$).

Discussion

An important study of tardive dyskinesia was that of Brandon *et al* (1971) who examined over 900 patients in a mental hospital. They looked in particular at the facial, bucco-linguo-masticatory dyskinesia (BLM) triad. Two findings emerged which are important. The first was that there was a marked increase with incidence of the syndrome with age, the highest incidence being in the 61-70 age group and remaining high after that age. The second was that the BLM triad existed in patients without a previous history of phenothiazine administration. The trend for an increased risk of dyskinesia with such a drug history was only significant amongst women over 70 years of age; this increase with age irrespective of drugs suggested a degenerative cause. It is then reasonable to consider the BLM triad as the basic syndrome and that other clinical groupings such as tardive dyskinesia, senile chorea, Huntington's chorea, and the dyskinesia associated with L-Dopa in parkinsonian patients, are syndromes arising out of pathological change (including response to chronic drug administration) in receptors and neurones within a particular neuronal circuit, lesions at various points (e.g. dopaminergic receptor supersensitivity, GABA neuronal degeneration) giving rise to very similar, if not identical, clinical pictures.

The first question to be answered in this present series is whether a significant degree of

TABLE II
Scores between two groups on the Withers and Hinton clinical test of sensorium and the paired associate learning test

Test	Tardive dyskinesia (n = 17)		No tardive dyskinesia (n = 33)	
	Mean	SD	Mean	SD
Orientation	6.4	1.7	6.4	1.3
Memory	43.7	9.7	44.1	11.8
Digits B.	6.4	4.7	5.8	3.0
Information (1)	6.9	5.2	6.6	3.6
Information (2)	5.1	4.0	4.0	2.4
Global	68.5	14.7	66.9	18.1
PALT†	26.4*	8.4 (n = 14)	20.0	6.8 (n = 25)

* Significantly different from controls $P < .05$, two-tail test

† Higher PALT scores indicate more impairment

TABLE III
Data from EMI scan measurements and neuroradiologist grading

EMI scan data	Tardive dyskinesia			No tardive dyskinesia		
	Mean	SD	n	Mean	SD	n
Radiological grading normal = 0	2.13	1.96	(15)	1.40	1.30	(30)
Huckman Number normal < 15	14.72	1.95	(11)	14.11	2.60	(26)
Ventricular index normal > 1.6	1.48	0.21	(10)	1.69	0.42	(26)
Cella media index normal > 4.0	3.84	0.61	(14)	3.86	0.67	(25)

No significant difference between groups

dementia was present. The group as a whole, on the psychological test of Withers and Hinton, achieved scores comparable with those chronic schizophrenics described by Johnstone *et al* (1978), and therefore fall into the range which exhibit organic impairment although only two of our patients were disoriented for age. There was, however, no difference on this test between those with and those without tardive dyskinesia. On the Paired Associate Learning Test a significantly higher number of the patients suffering from tardive dyskinesia were demented than in the control group. Learning tests have been found to be sensitive in early dementia and have been successfully used to detect dementia in patients undergoing renal dialysis (English *et al*, 1978). The original finding that patients suffering from chronic schizophrenia are significantly intellectually impaired is thus confirmed and there is a strong suggestion from the results of the learning test that the degree of dementia is greater in those patients with tardive dyskinesia.

On the evidence of the EMI scan there is again a substantial amount of abnormality demonstrated. Of the whole group, the radiologist's view was that in terms of either cortical atrophy or ventricular dilation 31 of the total of 45 showed pathological change. The whole group was in the pathological range on the cella media index. The degree of pathology scored from the neuroradiologist's report was found to correlate with the PALT scores. Using either the Huckman number, the cella media index or the ventricular index, 24 of 37 were found outside the reported normal range (Meese *et al*, 1976).

The radiologist's assessment did not differentiate between the two groups nor did the Huckman number and the cella media index. However, the ventricular index showed proportionately significantly more abnormal scans in the group with tardive dyskinesia. The study of Trimble and Kingsley (1978) failed to confirm an abnormality on EMI scan in a group of schizophrenic patients but they were younger (mean age 34 years) than our patients and some of them had been treated as out-patients.

As we could not assess the total drug consumption over the years in our patients, currently prescribed drugs, when compared, showed that the tardive dyskinesia group had received a significantly higher dosage of depot preparations. The dementia did correlate with the duration of treatment but as there was also a correlation of dementia with age, when this was partialled out, the influence of the duration of treatment just reached borderline significance and therefore possibly related to the intellectual deterioration (Marsden, 1976). Although age correlated with the global score on the tests of Withers and Hinton and Huckman number, the fact that the with and without tardive dyskinesia groups were matched for age rules this out as a cause of the difference between them. Thus, in agreement with the psychological test, an EMI scan finding suggests the tardive dyskinesia group have more observable pathology.

The association between tardive dyskinesia and brain damage has been made previously (Edwards, 1970). It should be noted that in that study the term 'brain damage' included not only evidence of organicity as defined by Shapiro *et*

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al (1956) but also defects on the word learning test of Walton *et al* (1959).

There are two possible explanations of these findings. The group of schizophrenics who remain in hospital are characterized by cerebral degeneration because of the nature of the illness and treatment with neuroleptic drugs causes tardive dyskinesia in those patients with greatest organic deficit. The second possibility is that the dementia occurring in schizophrenia is due to neuroleptic drugs and that tardive dyskinesia is an index of neuronal degeneration, and is prone to occur more frequently in the presence of such degeneration. This need not, however, be true for all the cases with tardive dyskinesia since some cases could be of pharmacological origin, i.e. dopaminergic supersensitivity due to drug-induced receptor blockade; these might be distinguishable by the time of onset after treatment and absence of intellectual deterioration. A further factor to be explored is that, given the patients have comparable doses of neuroleptics, is the individual variation in the metabolism of neuroleptic drugs—a factor which determines the onset of tardive dyskinesia? More research into this matter is required and also whether patients with other diagnoses, such as intractable cases of manic-depressive psychosis with an equally long drug history, also show evidence of dementia and EMI scan changes.

Should these findings be confirmed radical changes in drug treatment policy are indicated. It would also cast some doubt as to the cause of any abnormal biochemical finding in post-mortem brain studies of schizophrenic patients.

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