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Basal ganglia abnormalities in tardive dyskinesia

Possible relationship with duration of neuroleptic treatment

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Abstract The purpose of the present study was to investigate CT abnormalities in tardive dyskinesia (TD) and to search for possible relationships with clinical data. A group of 30 psychotic patients (15 schizophrenic and 15 affective disorder) with TD was compared to a matched group of 30 psychiatric patients without TD and a matched group of 30 healthy controls. CT data were analyzed using two multivariate statistical methods [multidimensional scaling (MDS) and step-wise discriminant analysis]. MDS clearly separated both TD and non-TD groups from the healthy control group on the basis of CT parameters. Caudate left area reduction and left temporal sulci enlargement were the most important parameters that discriminated TD from non-TD patients. Only in TD-patients did caudate left area reduction and left temporal sulci enlargement correlate significantly with cumulative duration of psychiatric hospitalizations. The data of the present study support the findings of structural abnormalities in the caudate nucleus and in the temporal lobe of patients with TD. These abnormalities were especially marked in the left hemisphere. It is assumed that some factor related to longer psychiatric hospital treatment (e.g. neuroleptic intake) could account for these abnormalities.

Key words Tardive dyskinesia · Computertomography Basal ganglia · Neuroleptic drugs · Schizophrenia Affective disorders

Introduction

Tardive dyskinesia (TD) is probably the most serious side effect of long-term neuroleptic exposure. The severity of TD resides in its potentially irreversible nature and in its medical and psycho-social complications (Yassa and Jones 1985).

Little is known of the processes which confer vulnerability to the emergence of TD. Risk factors for TD that have been consistently identified are advanced age and female gender (Yassa and Jeste 1992). Other factors that seem to play an important role are previous brain damage (Wolf et al. 1982), diagnosis of an affective disorder (Rush et al. 1982; Yassa et al. 1984) and high neuroleptic doses (Muscettola et al. 1993).

Because of its close relationship to neuroleptic exposition and high similarity to neurological syndromes, it is likely that TD involves an alteration of brain function. Moreover, because of its potentially irreversible nature, a structural brain abnormality might be present. Nevertheless, the neural mechanism underlying the development of TD remains poorly understood (Lohr et al. 1986), particularly with regard to the relative contributions of neuroleptic treatment and of the basic disease process itself to its pathogenesis (Owens et al. 1982; Waddington 1987).

A number of postmortem studies have indicated structural brain abnormalities in TD patients. Christensen et al. (1970) conducted a well-controlled study comparing the brains of 28 patients with TD with those of 28 patients without TD, matched for psychiatric diagnosis. They found that TD patients had macroscopically more cortical atrophy and larger ventricles and microscopically markedly more cell degeneration in the substantia nigra and gliosis in middle brain and brain stem. In a histological study, Jellinger (1977) compared the brains of nine patients with a functional psychosis and TD with those of 14 functional psychosis patients without TD. He found swelling of the great neurons and glia satellitosis in nuclei caudate in five TD patients and in only one psychiatric control.

CT and MRI Morphometric Studies

Since Gelenberg (1976) first investigated TD patients with CT, a number of authors have tried to identify structural

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abnormalities related to this disorder. Hoffman and Casey (1991) performed a metaanalysis of 18 CT reports on TD, focusing on VBR values among patients with and without TD. They concluded that although there is a trend in the direction of larger ventricles in TD samples, it is not of statistical significance.

In a review of 28 CT studies of TD, we observed that only 11 studies reported significant differences between TD patients and matched psychiatric patients without TD, whereas the majority of reports ($n = 17$) did not find significant differences (Table 1). These contradictory findings may be at least in part ascribed to the methodological shortcomings of some studies (small samples, few CT variables considered, and use of linear measures only) and to the heterogeneity of the samples with regard to catamnestic parameters and intensity of TD.

The purpose of the present study was to examine possible CT abnormalities related to TD in major affective disorder and schizophrenic patients. By means of a comprehensive CT assessment, we compared a TD group to a rigorously matched sample of psychiatric patients without TD, in order to exclude CT abnormalities not specifically related to the motor disorder itself. Moreover, we compared both TD and non-TD groups with a matched healthy control group to evaluate the influence of the psychiatric disorder.

Table 1 Computertomographic studies in tardive dyskinesia[a]

Brain area	TD patients with CT abnormalities	No significant differences
Enlarged lateral ventricles (VBR, ventricular index, cella media index)	6[a]	17
Frontal horn (frontal horn VBR, Huckman's number and bifrontal/bicaudate ratio)	2	9
Third ventricle (third ventricular width)	1	5
Cortical atrophy (inspection)	1	7
Area or volume of basal ganglia (caudate nuclei, lentiformis nuclei and globus pallidus)	2	–

[a] Number of studies

Methods

Patients and controls

The sample comprised 30 patients (15 major affective disorder patients and 15 schizophrenics) with tardive dyskinesia (TD), 30 psychiatric controls without TD, and 30 healthy individuals. Each TD patient was individually matched to a psychiatric control by age, gender, educational level, body height and weight, psychiatric diagnosis, age at onset and duration of illness, and number and cumulative duration of hospitalizations. The two patient groups were also individually matched to a healthy control group by age and gender. The demographic and clinical characteristics of patients and controls are depicted in Table 2. The cumulative duration of hospitalizations was apparently higher in patients without TD, but this difference was not statistically significant ($P > 0.15$) and was due to greater intragroup variability among patients without TD.

Psychiatric diagnosis was done according to DSM-III-R criteria. Tardive dyskinesia was diagnosed according to the criteria defined by Schooler and Kane (1982) and intensity of TD was assessed with the Abnormal Involuntary Movements Scale (AIMS). TD patients had a mean AIMS score of 13.2 ± 5.0. Clinical history and demographic data were obtained through a structured interview and completed with a careful chart review to assure reliability.

Table 2 Socio-demographic and clinical data in patient groups and healthy control controls ($x \pm y$ = mean ± standard deviation)

Group	Patients with TD	Patients without TD	Healthy controls
N	30	30	30
Age	55.1 ± 17.6	54.5 ± 17.5	54.8 ± 17.6
Gender (female/male)	23/7	23/7	23/7
Years of school	9.4 ± 2.0	9.4 ± 2.7	10.9 ± 4.6
Body height	1.64 ± 0.08	164 ± 0.07	1.67 ± 0.11
Body weight	70.6 ± 13.2	68.2 ± 11.1	68.2 ± 7.4
Diagnosis (major affective disorder/ schizophrenia)	15/15	15/15	–
Age at onset	42.7 ± 17.2	42.3 ± 18.4	–
Duration of Illness (years)	11.4 ± 10.4	10.0 ± 10.6	–
Number of hospitalizations	4.7 ± 3.9	4.6 ± 7.3	–
Cumulative duration of hospitalizations (months)	7.5 ± 5.7	12.2 ± 24.1	–
Neuroleptic doses[a]	240 ± 246	174 ± 208	
Antidepressant doses[b]	61 ± 74	106 ± 51	

[a] Daily doses in schizophrenic patients in chlorpromazine equivalents
[b] Daily doses in affective disorder patients in imipramine equivalents

CT Measurements

CT scans were performed on a fourth-generation Siemens scanner (SOMATOM DRH). Patients were positioned in a rigid head holder and a scout film was used to adjust the scanner to the desired position. Each scan consisted of 12–14 cuts taken in 8-mm steps parallel to the orbitomeatal line. All the scans were non-enhanced. The window on all the scans had a width of 128 and a center of 40 HU. For our measures, we used the slices from the lower third ventricle level up to one slice above the cella media.

The scan films were then projected onto a screen with an overhead projector and were enlarged to the brain's original size (1:1). Linear measurements were subsequently performed with a transparent ruler (Mark Rotring, type 801 030, precision 0.5 mm). Area measurements were performed with a fixed-arm manual planimeter (Mark Haff, Type 317 E, precision 0.1 cm^2, for an area of 100 cm^2 accuracy better than 0.2%). Accompanying this planimeter is a transparency with a designed ellipse that contains an area of exactly 100 cm^2. After every five measurements, the precision of the instrument was reconfirmed against this standard area.

At the level of their widest diameter or area, we performed the following measurements:

1. Linear measurements of sylvian fissure left (L) and right (R), temporal sulci L and R, parietal sulci L and R, frontal sulci L and R, and interhemispheric fissure.

2. Planimetric measurements of brain area (at the level of the Foramen Monroe), third ventricle VBR, frontal horn VBR, lateral ventricles VBR, caudate head area/brain area ratio and nucleus lentiformis area/brain area ratio.

Interrater and test-retest reliability were blindly established for a random set of 20 scans with a Spearman rank correlation of 0.89–0.97 for planimetric measurements and of 0.80–0.99 for linear measurements. The reliability of this method in comparison to a computer-assisted method (Siemens, Evaluskop, Version EVA 1) was also blindly established for a random set of 25 cases for the lateral ventricle VBR. The Spearman rank correlation was for lateral ventricle VBR 0.94.

All CT measures were performed blindly with respect to subject status (TD diagnosis, psychiatric diagnosis, age etc.).

Statistical analysis

The CT variables from the whole sample were simultaneously analyzed by multidimensional scaling (MDS), as is throughly described elsewhere (Gattaz et al. 1988). Briefly, to be comparable, the 16 CT parameters (see Table 3) were standardized for all subjects such that the standard deviation with respect to the control group equalled 1. The full data set can be considered as a cloud of points consisting of the 90 subjects (30 TD and 30 non-TD patients, as well as 30 healthy controls) in the 16-dimensional parameter space. MDS seeks a two-dimensional (i.e. low-dimensional) representation of this 16-dimensional cloud of points, while retaining as much as possible the distances between the subjects. No information about the composition of the groups is used. The MDS algorithm is based on the ranking of the distances, and this lowers the influence of an aberrant value in some dimension. The results presented here are based on the algo-

Table 3 Computed tomographic (CT) parameters in patients with tardive dyskinesia (TD), in matched patients without tardive dyskinesia, and in healthy controls (VBR = ventricular/brain ratios; BsGg = structures of the basal ganglia)

CT Measures	Patients with TD (n = 30)	Patients without TD (n = 30)	Healtyh controls (n = 30)
VBR			
Third ventricular VBR	1.16 ± 1.49*	0.78 ± 0.40**	0.56 ± 0.33
Frontal horn VBR	3.25 ± 1.33**	2.82 ± 1.14*	2.27 ± 0.89
Lateral ventricular VBR	9.22 ± 4.05*	8.52 ± 3.25*	7.16 ± 2.62
BsGg			
Caudate/brain ratio L	0.71 ± 0.16*** °°°	0.81 ± 0.16***	0.83 ± 0.17
Caudate/brain ratio R	0.72 ± 0.18***	0.78 ± 0.12***	0.84 ± 0.14
Lantiformis/brain ratio L	2.22 ± 0.52	2.29 ± 0.51	2.19 ± 0.49
Lentiformis/brain ratio R	2.13 ± 0.53	2.09 ± 0.44	2.00 ± 0.40
CORTEX			
Sylvian fissure left	5.4 ± 1.1**	5.8 ± 2.2**	4.1 ± 2.0
Sylvian fissure right	5.0 ± 1.9***	5.0 ± 2.1***	3.5 ± 1.5
Temporal sulci left	1.9 ± 2.7°°°	0.8 ± 0.9	1.0 ± 0.9
Temporal sulci right	1.1 ± 1.3°	0.7 ± 1.0	0.8 ± 0.8
Parietal sulci left	2.7 ± 1.2*** °	2.1 ± 1.0	1.8 ± 1.3
Parietal sulci right	2.4 ± 1.3***	2.2 ± 1.1*	1.5 ± 1.2
Frontal sulci left	3.2 ± 1.6	2.7 ± 1.1	2.6 ± 1.5
Frontal sulci right	3.1 ± 1.3	2.8 ± 1.1	2.6 ± 1.2
Interhemispheric fissure	3.6 ± 1.4	3.4 ± 1.3	2.8 ± 2.0

* $P < 0.05$; ** $P < 0.01$; *** $P < 0.005$ (differences between patients and healthy controls)
° $P < 0.05$; °° $P < 0.01$; °°° $P < 0.005$ (differences between TD and non-TD groups)

rithm ALSCAL. To characterize the normative region occupied by the control group, (1-p)-convex hulls were introduced: a convex hull of a two-dimensional cloud of points is the region defined by its exteme points and the straight lines between them. To obtain the (1-p)-convex hull, a proportion (p) of the most extreme subjects is eliminated, such that the area covered becomes minimized (p = 1/30 in the present study). The patients outside the normative region represent a conspicuous subgroup compared to those inside. This is a formal quantitative definition which does not assign a "pathological label" (e.g. "atrophy") to some deviation. The method presented bears a relation to techniques such as discriminant and cluster analysis. One feature peculiar to MDS is that a graphic analysis is important, which allows further insight into the composition of groups: especially in the case of CT parameters, it seems to us that transition zones are more common than distinct subgroups, and that they may perhaps be better judged visually than by a formal algorithm forcing subgroups to be homogeneous (as in cluster analysis).

As dimensions 1 and 2 represent a high-dimensional space, they should both be thought of as factors with some relationship to each of the parameters. In contrast to factor analysis, the relationship between parameters and dimensions is not linear but implicit. We have therefore not attempted to give a meaning or even a neuroanatomical relevance to the dimensions in MDS, since this might be too speculative.

Jackknifed discriminant analysis and non-parametric tests for group comparisons (Wilcoxon test) were also performed. Because age correlates strongly with CT parameters, the effect of age within groups was partialized out and partial Spearman rank correlation coefficients were calculated. The adopted level of significance was 5%.

Results

Figure 1 provides a two-dimensional representation of all 90 subjects for all CT parameters obtained by MDS. The normative region is defined by the 29/30-convex hull of the control group and thus encompasses 96.7% of the controls. This normative region allowed a total separation between patients with tardive dyskinesia and healthy controls. It also shows a clear separation between patients without TD and healthy controls and a discrete but noticeable discrimination between patients with TD and patients without TD.

Discriminant analysis showed that the caudate/brain ratio left alone discriminated correctly 63.3% of the patients with TD in relation to patients without TD. Only with the eight following parameters that entered into the stepwise discriminant analysis (sylvian fissure left, temporal sulci left, frontal sulci left, third ventricle VBR, brain area, lateral ventricle VBR, and parietal sulci left) was a discrimination level of 70.0% reached. For the groups "patients with TD" and "healthy controls", the sylvian fissure right, nucleus lentiformis/brain ratio right, and the caudate/brain ratio right allowed a discrimination

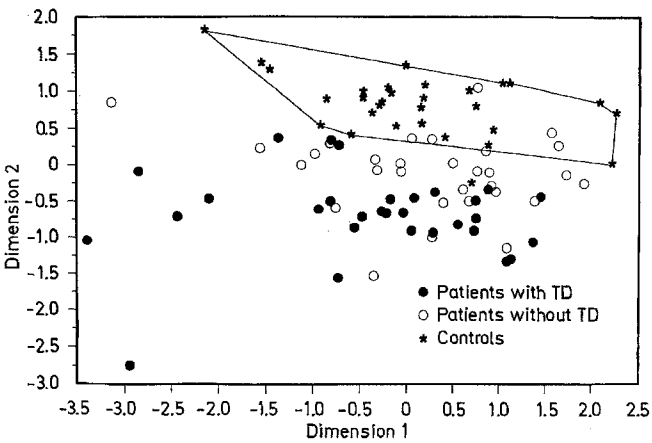

Fig. 1 Two-dimensional representation of 17 computertomographic parameters obtained by multidimensional scaling

of 70.0%. For the groups "patients without TD" and "healthy controls", the parameters sylvian fissure right, temporal sulci left, and parietal sulci right could correctly discriminate 73.3% of the patients.

TD patients had a significantly larger temporal sulci left and smaller caudate area/brain area ratio left, than non-dyskinetic patients (Table 3). When these comparisons were done for the schizophrenic and affective patients separately, the differences in caudate/brain ratio remained significant for both groups.

Only in TD patients did we find negative correlations between cumulative length of hospitalization, on the one hand, and caudate area/brain area left ($r = 0.58$, $P < 0.005$) and the temporal sulci left ($r = 0.47$, $P < 0.01$), on the other. No consistent correlations were found between AIMS total score and CT parameters.

Discussion

At the outset, it is wise to stress that the present results must be interpreted with caution, as type-I errors are not unlikely in the face of the relatively large number of CT parameters investigated. However, because the use of more conservative methods (e.g. Bonferroni correction) may cause the loss of meaningful relationships, we opted for a discussion based mainly on the general picture of the findings and on the plausibility of the results in connection with data from the literature.

The results of the multivariate analyses demonstrated significant structural brain abnormalities in patients with TD in comparison to matched psychiatric and normal controls. MDS provided a full discrimination between TD patients and normal controls and an almost complete one between non-TD patients and normal controls. The latter is in line with a vast literature (see metaanalysis in Raz and Raz 1990) demonstrating consistent structural brain abnormalities in both schizophrenic and major affective patients. Although TD patients also tended to be discriminated from non-TD patients, a considerable overlap was

found between these two groups. As our samples of dyskinetic and non-dyskinetic patients were rigorously matched for clinical and demographic variables, it is likely that the CT differences observed are related to the TD.

The nucleus caudate/brain ratio on the left side alone could correctly discriminate 63.3% of cases with and without TD. This finding is of interest as other involuntary movement disorders, such as Huntington's chorea, Wilson's disease, and Athetosis syndrome, which share similar symptoms with TD, show unquestionable structural abnormalities in the basal ganglia (Lohr et al. 1986). Two studies (Bartels and Themelis 1983; Mion et al. 1991) examined in schizophrenic patients basal ganglia-structures with planimetric or volumetric methods and found significant striatum reductions in TD patients. We replicated these previous findings and demonstrated that caudate reduction is present to the same extent in affective patients with TD.

In agreement with the discriminant analysis, the univariate comparisons indicated the presence of temporal sulci enlargement in the TD group. Previous studies (Sandyk and Kay 1991; Stuckskstedte et al. 1984) focussed on higher slices to examine cortical sulci enlargement and thereby lost the evaluation of temporal sulci. The data of the present study indicate that the temporal lobe in TD subjects should be investigated more carefully in the future.

In the TD group, reduction of left caudate head area and of temporal sulci width were related to cumulative length of hospitalization. Conversely, in the non-TD group, there were no correlations between cumulative length of hospitalization and CT parameters; in fact, the data tended in the opposite direction. These findings indicate that in the brains of TD patients, the basal ganglia are especially vulnerable to some factor related to the cumulative length of hospitalization, such as the total amount of neuroleptic intake during the course of the disease.

Recent animal studies have demonstrated neurotoxic cell damage in the striatum, especially in the large neurons of the caudate nuclei, after long-term neuroleptic exposition (Mahadik et al. 1988; Meshul and Casey 1991; Jeste et al. 1992). In a postmortem study, Gross and Kaltenbäck (1970) found a significant correlation between duration of neuroleptic exposition and gliosis, satellitosis, and neuronophagia in the caudate nuclei. Based on these data, it is plausible to speculate that in vulnerable subjects, long-term neuroleptic exposition (associated with the cumulative length of hospitalization) may play a relevant role in the caudate head reduction, thus facilitating the onset of TD.

However, an alternative hypothesis is that CT abnormalities are already present before the onset of TD. Since controlled studies (Gattaz et al. 1988; Weinberger et al. 1980; Luchins et al. 1984) have demonstrated that patients with previous CT abnormalities are less responsive to current neuroleptic treatment, it is likely that this group will need higher neuroleptic doses to achieve psychosis' remission. Recently, Muscettola et al. (1993) identified in a large (n = 1745 patients) epidemiologic study that high neuroleptic dose is significantly associated with increased risk of TD. In addition, there is some evidence that neuroleptics tend to have more deleterious effects on previously damaged neural tissue (Chouinard et al. 1979). These data could also explain the correlation between cumulative length of treatment and caudate head reduction observed in our TD patients.

Although both heads of caudate were smaller in TD patients, only on the left side were statistically significant differences found. Moreover, the strong negative correlation with cumulative length of hospitalization was found only in the left caudate. The temporal sulci enlargement found in the TD group was also more pronounced in the left hemisphere. This lateralization is in line with the findings of Bartzokis et al. (1990), who, using MRI T2 relaxation times, found shortened left (but not right) caudate head T2 in TD patients, compared to a non-TD sample.

Although the existence of a side preponderance for neuroleptic-induced involuntary movements is still controversial (Altshuler et al. 1988), most studies have favored a preponderance of right-sided movements (Waziri 1980; Wilson et al. 1984; Caligiuri et al. 1989; Sachdev 1992), indicating that the left striatum may be more involved in the pathophysiology of involuntary movements than the right one. One conceivable mechanism for the greater sensitivity of the left striatum and left temporal lobes may concern the amount of blood flow and related availability of neuroleptics acting in these structures (Myslobodsky and Weiner 1976). Because elevated neuronal activity in a particular area of the brain induces greater blood flow (Oleson 1971; Haxby et al. 1991), in the right-handed individual, the left striatum would be more active and have more blood flow (all but one of our TD patients were right-handed). This seems also to be valid for the temporal lobes and particularly marked in schizophrenic patients. DeLisi et al. (1989), using PET scan, reported relatively higher left temporal lobe metabolic rates in schizophrenics than in controls during sensory stimulation of the right arm. Therefore, it is plausible that long-term neuroleptic exposition could damage preferentially left-sided structures in vulnerable subjects.

In conclusion, we found that brain structural abnormalities discriminated TD patients from psychiatric and healthy controls. These abnormalities were more evident in the basal ganglia and correlated with the cumulative duration of psychiatric hospitalizations. Further prospective studies should clarify whether TD patients have a higher vulnerability to the damaging effects of neuroleptics on brain structures or whether previously existing brain structural abnormalities confer a higher vulnerability to TD.

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