Arch Psychiatr Nervenkr (1983) 233 : 371–379

Archiv für Psychiatrie und Nervenkrankheiten
Archives of Psychiatry and Neurological Sciences

Computerized Tomography in Tardive Dyskinesia

Evidence of Structural Abnormalities in the Basal Ganglia System

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Summary. Twenty-nine patients with moderate to severe tardive dyskinesia (TD) and 29 age- and sex-matched controls (C) with long-term neuroleptic therapy comparable to that of the patients were all examined using computerized tomography. Significant differences were found between the two groups in the width of the third ventricle (TD > C), the bicaudate distance (TD > C), the computed area of the head of the caudate nucleus (TD < C), and the area of the lenticular nucleus (TD < C). No significant differences were established in the ventricular or cella media indices. These results suggest that structural abnormalities, primarily in the basal ganglia system, are present in TD patients. Psychological testing with the Benton visual retention test also showed significant differences with regard to cerebro-organic functional impairment among TD patients.

Key words: Tardive dyskinesia – Computerized tomography – Basal ganglia

Introduction

Tardive dyskinesia (TD) is the most important complication of long-term neuroleptic therapy. Guarded estimates suggest that the prevalence of persisting dyskinesia is approximately 13% (Jeste and Wyatt 1981), i.e., a considerable number of patients worldwide suffer from this syndrome, which up to now has responded poorly to any form of therapy. In addition to all the other unanswered questions primarily concerning epidemiology and biochemistry, pre-existing cerebro-organic damage, particularly in the basal ganglia system, is discussed as one possible factor contributing to the appearance of TD.

Our computerized tomography (CT) study was designed to answer a question also posed by other authors: does pre-existing brain damage increase the incidence of TD? CT is still the best in vivo method for detecting structural abnormalities in the brain. Earlier investigations dealing with this question

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(Gelenberg 1976; Jeste et al. 1980; Famuyiwa et al. 1979), some using qualitative (Gelenberg), some quantitative (Jeste et al. 1980, Famuyiwa 1979) measurements, found differences between TD patients and matched controls that tended to support the above hypothesis. These differences, however, were not statistically significant. The measurements were usually limited to classic neuroradiologic parameters and/or indices. Our study was set up as follows. The neurologic data of a satisfactorily large number of TD patients and matched controls were evaluated as exactly as possible using the AIMS scale. The neuroradiologic measurements were done by two experienced neuropsychiatrists. In addition to the classic neurologic measurements (distances and distance ratios), the structures in question, with damage and/or pre-existing damage, particularly in the basal ganglia system, were measured as exactly as possible with computer-assisted methods.

Methods

Selection of Patients

A total of 58 patients were subjected to psychiatric, neurologic, and neuroradiologic examination as well as psychological testing. All patients were long-term residents of the Rottenmünster Psychiatric Hospital. The findings are presented in Table 1.

The symptoms of 29 patients with moderate to severe TD were assessed using the method developed by Gerlach (1976) and ranked according to a scale for abnormal involuntary movements (AIMS). For each TD patient, an age- and sex-matched control on long-term neuroleptic therapy but without signs of TD was subjected to the same examinations. The mean AIMS score for the TD patients was 15.66 ± 3.29, i.e., moderate to severe TD. Parallel to the AIMS evaluation, the somatotopic distribution pattern was also determined. The results indicated that involuntary movements of the extremities and/or trunk, in addition to orofacial dyskinesia, were present in 14 of the 29 TD patients. The Benton visual retention test (instruction C) was given and scored on the basis of the number of correct reproductions. During the course of the examination, it became obvious that a differentiated evaluation was not expedient because of the low performance level of most of the patients.

The neuroradiologic examination was carried out with a computer tomograph (Siemens, Siretom 2000). Prior to the CT examination, a mild sedative (10 mg Tranxilium [chlorazepate dipotassium] IM) was administered to some patients to reduce anxiety. The neuroleptic dosage was temporarily slightly increased a few days prior to the examination to minimize dyskinetic phenomena and ensure a minimum of movement artefacts on the scans. The orbitomeatal line (OM line) was taken as the plane of reference. An average of 5 or 6 axial sections were made per patient, starting with section "O" in the OM line and moving 10 mm apically for each new section. Specific parameters were evaluated using a PDP computer with corresponding programs (Siemens, Evaluskop, Version Eva). The following structures were visualized, using intermediate sections when necessary (see also Figs. 1, 2):

1. Maximal width of the third ventricle
2. Head of caudate nucleus (to determine area)
3. Lenticular nucleus (to determine area)
4. Maximal width of anterior horns of the lateral ventricle and minimal distance between both caudate nuclei
5. Distance of lateral ventricle on the cella media section (minimal width of cella media)
6. Distance between both choroid plexuses.

All distances were measured in millimeters, using an Evaluskop program designed for this purpose. An appropriate program was used to measure areas; the areas of the traced structures were presented in square millimeters. All measurements were made "blind", i.e., without knowledge of the individual data or of the group to which the patient was assigned.

Table 1. Diagnostic, pharmacotherapeutic, neurologic and psychological variables of the samples

	Tardive dyskinesia	Age- and sex-matched controls
n, (age/mean)	29, (65.8 ± 10)	29, (63.5 ± 9)
Sex	22 women/5 men	22 women/5 men
ICD	295.6 = 22	295.6 = 20
Diagn.	295.7 = 3	295.7 = 7
9th revision	297.0 = 4	297.0 = 2
NL therapy (years)	21.39 ± 4.6	23.04 ± 5.2
AIMS score	15.66 ± 3.29	–
Somatotopic	BLM[a]: 29	–
distribution	+ extremities and trunk: 14	–
	Average and below average	2 3
	Limit	1 4
Benton visual retention	Impaired performance	4 6
	Severely impaired performance	22 9

[a] BLM: bucco-linguo-masticatory syndrome

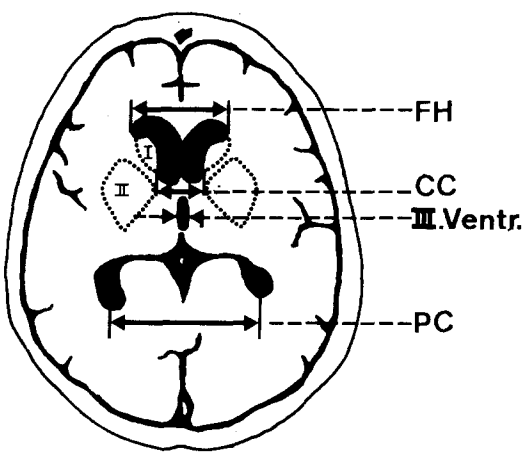

Fig. 1. Neuroradiologic measurements. Abbreviations as in Table 2

Results

As the following parameters show, statistically significant differences existed between the two groups (see Table 2).

The difference between the mean values for the shortest distance between both anterior horns of the lateral ventricle at the caudate nucleus in TD patients

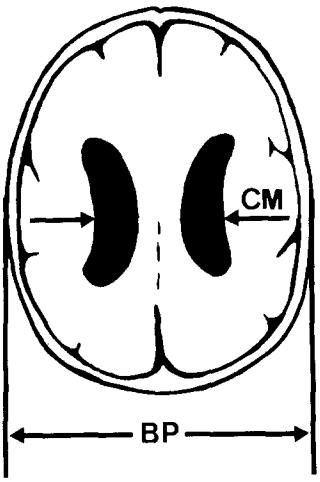

Fig. 2. Neuroradiologic measurements. Abbreviations as in Table 2

Table 2. Results of neuroradiologic measurements

	Tardive dyskinesia	Age- and sex-matched controls	Level of significance
CC	17.48± 4.7 mm	15.1 ± 3.87 mm	$P<0.05$
III.V.	7.66± 2.29 mm	6.34± 2.14 mm	$P<0.05$
CD li	87.55±33.1 mm^2	105 ±39.02 mm^2	$P<0.05$
CD re	86.31±27.14 mm^2	101 ±32.42 mm^2	$P<0.05$
CLP li	219.45±61.26 mm^2	264.86±69.94 mm^2	$P<0.01$
CLP re	223.79±68.02 mm^2	283.52±77,74 mm^2	$P<0.01$
FH/CC	1.93	2.16	$P<0.1$ NS
VI	1.45	1.45	NS
CMI	5.12	5.2	NS

List of abbreviations used:

CC: Minimal distance of both nuclei caudati

CD: Area of head of caudate nucleus (I in Fig. 1)

CLP: Area of lenticular nucleus (II in Fig. 1)

CM: Minimal width of cella media

FH/CC: Ratio between maximal and minimal frontal horn distance (Neophytides et al. 1979)

CMI: Cella media index

VI: Ventricle index

(17.48±4.7 mm) and the controls (15.1±3.87 mm) was statistically significant at the 5% level. Similarly, the difference between the mean values for the width of the third ventricle in the TD patients (7.66±2.29 mm) and in the controls (6.34±2.14) was statistically significant at the 5% level. The mean values for the area of the head of the caudate nucleus in TD patients were 87.55±33.1 mm^2 (left) and 86.31±27.14 mm^2 (right) and in the controls 105.0±39.02 mm^2 (left)

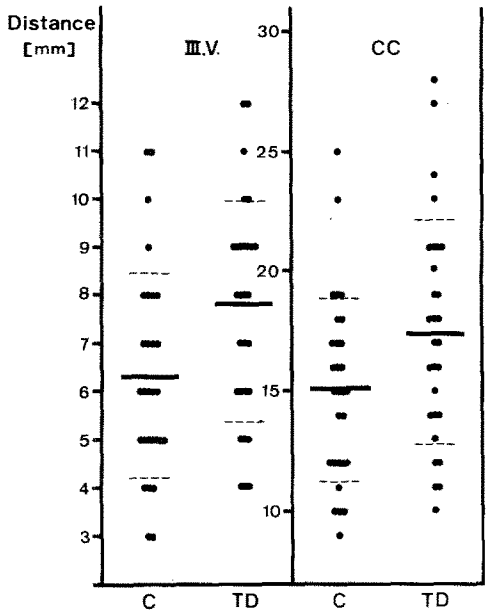

Fig. 3. Maximal width of the third ventricle (*III.V.*) and the minimal distance of both caudate nuclei (*CC*) in patients with tardive dyskinesia (*TD*) and controls (*C*); mean and standard deviation

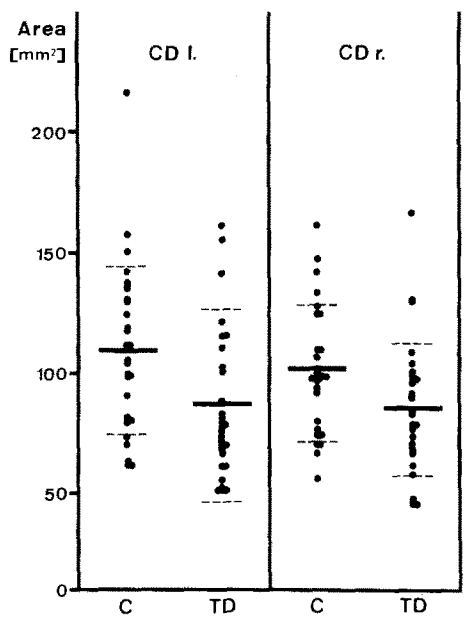

Fig. 4. Area of head of caudate nucleus (*CD*) of both sides in patients with tardive dyskinesia (*TD*) and controls (*C*); mean and standard deviation

and $101.9 \pm 32.42\,mm^2$ (right). The difference between the mean values for both sides was statistically significant at the 5% level. Comparison of the areas of the lenticular nucleus also showed significant differences at the 1% level. The mean values for the corresponding areas in TD patients were $219.45 \pm 61.26\,mm^2$ (left) and $223.79 \pm 68.02\,mm^2$ (right); in the controls, $264.86 \pm 69.94\,mm^2$ (left) and $283.52 \pm 77.74\,mm^2$ (right).

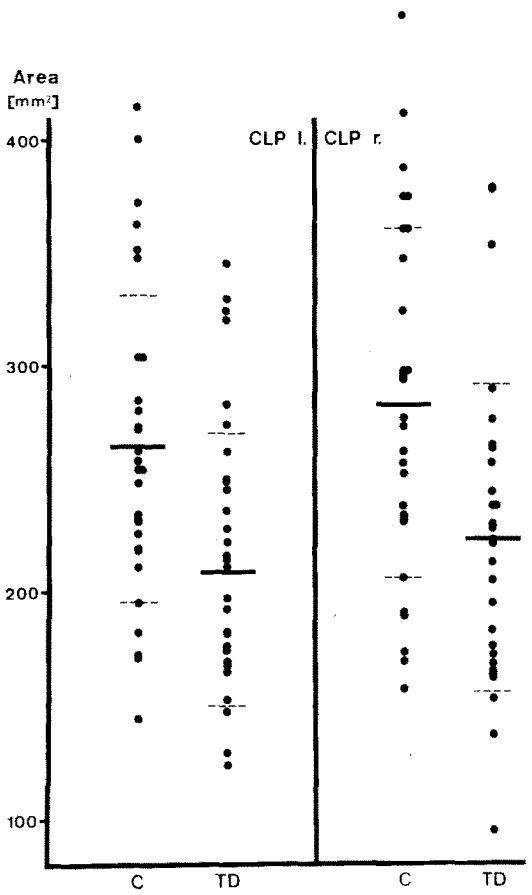

Fig. 5. Area of lenticular nucleus (*CLP*) of both sides in patients with tardive dyskinesia (*TD*) and controls (*C*); mean and standard deviation

The mean maximal widths of the anterior horns of the lateral ventricle differed as well (TD patients, 1.93; controls, 2.16); the difference, however, was not statistically significant. The ventricle and the cella media indices for both groups were almost identical (1.45 and 1.45, 5.12 and 5.20).

Correlations

The duration of neuroleptic therapy and all other parameters in which the TD patients differed significantly from the control group were correlated with the severity of dyskinesia (as determined by the AIMS score). None of the correlations showed any significant relationships ($r<0.2$) in any of the cases.

Statistical Evaluation

The groups were compared with the *t*-test for independent random samples. In the absence of a normal distribution (CD), significance was determined with the Mann-Whitney *U*-test.

Discussion

TD syndrome is of considerable clinical and theoretical importance. In contrast to neuroleptic-induced parkinsonism, the clinical picture of which resembles that of Parkinson's disease, TD developing after prolonged neuroleptic therapy seems to be related clinically to Huntington's chorea. The attempt was made, therefore, to identify similar morphologic, neuropathlogic, and biochemical mechanisms. The CT study of 8 TD cases carried out by Gelenberg (1976), however, was more quantitative than qualitative, in terms of method, and found no apparent structural abnormalities. This finding, however, disagrees with the neuropathologic findings reported by Gross and Kaltenbäck (1969). Using histologic methods, they demonstrated marked atrophy of the caudate nucleus in 3 TD patients. Neuropathologic examination of 28 brains by Jellinger (1977) from patients with prolonged use of neuroleptics, 14 of whom had TD, showed histologic alterations (increased satellitosis and gliosis, predominantly in the caudate nucleus, indicative of cellular degeneration). A markedly higher incidence of such neuropathologic alterations was found in the TD group (57%) than in the control group of patients on long-term neuroleptic therapy but without clinical signs of TD (37.5%).

In many cases, gross examination of the brains of TD patients showed "cortical atrophy and ventricular dilation" (Christensen et al. 1970). "more atherosclerosis of the basal cerebral arteries, and an increased incidence of minor infarcts in the anterior part of the striatum and/or frontal lobes" (Kameyama et al. 1975).

In a qualitative assessment of CT scans, Famuyiwa et al. (1979) found more signs of inner atrophy on scans from TD patients than on those from the controls. More signs of dementia were observed in the TD group than in the control group. Jeste et al. (1980) examined 12 TD patients and age-matched controls of different standard sizes; the ratio between the widest distance between the anterior horns of the lateral ventricle and the shortest distance between both caudate nuclei in TD patients was smaller than that in the control group, but not statistically significant. Nevertheless, Jeste observed morphologic alterations similar to those reported by Neophytides et al. (1979) in patients with Huntington's chorea. Our examinations of 29 TD patients showed significant differences between TD patients and controls in terms of: (1) the shortest distance between both anterior horns of the lateral ventricle; (2) the width of the third ventricle; (3) the area of the head of the caudate nucleus and of the lenticular nucleus, as determined by planimetric methods.

Planimetric measurements showed these significant differences in both hemispheres. The method used for obtaining areal measurements is not without problems. Difficulties arose in connection with the definition of the nuclear regions, particularly the recording of the lenticular nucleus. The relatively broad scattering for the groups is due primarily to the difficulty in defining the nuclear region and to the fact that both standard and intermediate sections included slightly different areas of the brain in each subject. Nevertheless, our statistically significant results indicate that our method of measuring two-dimensional parameters (areas) is more suitable for detecting atrophy than are pure distance measurements.

Perris et al. (1979) and Edwards (1970) also reported a considerably higher incidence of anamnestically and apparatively (CT scan, EEG) demonstrated pre-existing brain damage among TD patients.

Our findings tend to indicate that structural alterations can be suspected in the basal ganglia of TD patients. The basal ganglia system is an integral part of the motor system. Experimental structural and/or morphologic alterations led to a number of motor disturbances, both hypokinetic (rarer) and hyperkinetic (more frequent). The fact that we, in contrast to other authors, obtained significant results which tend to support the hypothesis, is, in our opinion, attributable to the comparatively large number of patients examined and to the exact neurologic review of the patient population. Since the patients were assessed without prior knowledge of individual data and/or the group to which they were assigned, the possibility of systematic measurement errors can, for the most part, be excluded.

The question, however, does arise as to whether the structural alterations found in TD patients are sequelae of long-term neuroleptic therapy, whether they represent pre-existing structural abnormalities or possibly a combination of both. To clarify this question, we calculated the correlation between the duration of neuroleptic therapy (in years) and the structural alterations, but no relationship whatsoever could be established. It is therefore more likely that dyskinetic phenomena associated with neuroleptic therapy develop on the basis of structural alterations. This finding also agrees with clinical observations of acute adverse effects (neuroleptic-induced parkinsonism, acute dystonic reaction, akathisia) in patients on long-term neuroleptic therapy: the incidence of such disturbances was usually markedly higher in patients with pre-existing brain damage (as determined by anamnestic data, CT, EEG) (Perris et al. 1979). Given these findings, close monitoring of patients with motor disturbances at the beginning of neuroleptic therapy seems advisable, since these patients are very possibly more prone to TD. These preliminary findings, however, will require further study, particularly to clarify whether, as we believe, TD is a disorder centered predominantly in the basal ganglia system. This question must be investigated further with more sophisticated neuopathologic, biochemical, neurophysiologic, and neuroradiologic methods.

Acknowledgements. We would like to express our gratitude to Dr. F. Eichstätter and Dr. J. Gestrich for providing the patients, to Dr. A. E. Schmidt for supplying the neurologic equipment, to Dr. D. Axmann as well as Mrs. I. Bauer and Mrs. H. Müller for the statistical analyses.

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Received July 5, 1983