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Relationship between Tardive Dyskinesia, L-Dopa-Induced Hyperkinesia and Parkinsonism

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Abstract. In a study of 16 psychotic patients with neuroleptic-induced tardive dyskinesia and 16 patients with Parkinson's disease and L-Dopa-induced hyperkinesia it was found that (1) tardive dyskinesia, compared to L-Dopa hyperkinesia, was localized almost exclusively to the oral region ($P < 0.01$), whereas the L-Dopa hyperkinesia was more pronounced in the neck ($P < 0.05$) and the extremities ($P < 0.05$); (2) L-Dopa hyperkinesia showed an increasing tendency to oral preponderance with age, irrespective of the severity of parkinsonism and extra-oral hyperkinesia, while tardive dyskinesia only itensified with age, without any change in distribution; and (3) extra-oral L-Dopa hyperkinesia was related to the localization and severity of pretreatment parkinsonism, and more to bradykinesia than to rigidity and tremor. It is concluded that the irreversible neurotoxic effect of neuroleptic drugs may be associated with age-related changes in the oral somatotopic region of the basal ganglia (to be given consideration in any future search for the pathogenetic process underlying irreversible tardive dyskinesia), and that the pathophysiology of involuntary hyperkinesia in neuroleptic-treated psychiatric patients and in L-Dopa-treated Parkinson patients may consist of a primary dopamine deficiency (pharmacological or structural), and a secondary relative hyperactivity in the dopaminergic system ("dopaminergic hypersensitivity") possibly corresponding to hypoactivity in the cholinergic system.

Key words: Tardive dyskinesia – L-Dopa-induced hyperkinesia – Parkinson's disease

Tardive dyskinesia is an involuntary, at times irreversible hyperkinetic syndrome which develops during or following neuroleptic treatment of psychiatric patients (Ayd, 1967; Crane, 1968, 1973; Klawans, 1973). Phenomenologically, this movement disturbance is of the same type as L-Dopa-induced hyperkinesia in patients with Parkinson's disease (Barbeau, 1969; Klawans, 1973).

The pathogenesis of these two types of hyperkinesia is still not fully elucidated. So-called dopaminergic hypersensitivity (Carlsson, 1970; Ungerstedt, 1971; Klawans, 1973) and/or cholinergic hypofunction (Birket-Smidt, 1974; Gerlach et al., 1974, 1976; Klawans and Rubovits, 1974) appears to be involved. Dopamine deficiency (parkinsonism) may be a prerequisite for the development of these involuntary movements (see below for references), and tardive dyskinesia is positively correlated to age (Crane, 1973).

In Parkinson's disease the neuroanatomical lesion consists mainly of a focal loss of dopamine neurons originating from the zona compacta of the substantia nigra and terminating in the striatum (Bernheimer et al., 1973). A corresponding organic defect underlying the irreversible tardive dyskinesia has not yet been found, possibly because we do not know where and what to look for. In spite of the difference in the pathophysiology, a comparison between the distribution of tardive dyskinesia and of L-Dopa hyperkinesia in Parkinson patients may provide an indirect picture of the approximate site and size of the pathogenetic process underlying the irreversible tardive dyskinesia.

In neither of the two types of hyperkinesia is the relationship between the hyperkinetic movements and the parkinsonism fully clarified. It has been shown that parkinsonism and tardive dyskinesia often coexist (Fann, 1974), that parkinsonism may precede the development of tardive dyskinesia (Crane, 1972), and that parkinsonian symptoms may be a primary and integrated part of tardive dyskinesia (Gerlach

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Table 1. The Parkinson patients, the main Parkinson symptoms and the L-Dopa-induced hyperkinesia

Pat. no.	Sex	Age	Characteristic of Parkinson's disease				Main Parkinson symptoms of the upper extremity			L-Dopa induced hyperkinesia		
			debut age	disab. stage	Webster score	unilat. symptoms	brady-kinesia	ridigity	tremor	oral	head	upper extremity
1.	f	47	38	IV	11	dxt	2	1	2	0	0	8
2.	m	49	33	IV	15	sin	3	1	3	1	1	9
3.	m	49	37	V	17	–	3	1	0	0	2	4
4.	m	49	39	IV	16	dxt	3	1	0	0	3	9
5.	m	51	45	III	12	–	2	1	1	1	3	4
6.	m	55	46	IV	18	dxt	3	1	2	2	1	6
7.	f	62	54	IV	17	sin	3	3	2	2	3	12
8.	f	63	52	IV	10	–	2	1	0	2	2	8
9.	m	65	64	II	9	–	2	1	2	3	0	0
10.	f	66	57	III	11	sin	2	2	2	2	1	0
11.	f	67	61	IV	13	–	2	1	3	0	3	8
12.	f	68	66	III	13	–	3	1	2	2	2	5
13.	m	70	62	III	12	–	1	0	1	3	2	1
14.	m	71	65	IV	14	–	2	0	2	2	3	6
15.	m	73	63	III	12	dxt	2	1	2	3	1	0
16.	m	74	72	III	12	dxt	1	0	2	4	2	3

Disability stage is estimated from 0 (no parkinsonism) to V (maximally disabled by parkinsonism) (Hoehn and Yahr, 1967).
Webster score represents total score according to the rating scale used (Webster, 1968).
Bradykinesia, rigidity and tremor are scored from 0 to 3. The *L-Dopa hyperkinesias* are scored as follows: the oral movements (tongue and mouth) from 0 to 6; head movements from 0 to 3; and upper extremity movements (shoulder, whole arm, elbow, wrist and fingers) from 0 to 15.

and Thorsen, 1976). However, as the degree of parkinsonism in patients with tardive dyskinesia is relatively slight, it might be more advantageous to study this relationship between hyperkinetic movements and parkinsonism in Parkinson patients with L-Dopa-induced involuntary movements. In those patients with asymmetrical parkinsonism, it has been shown that the L-Dopa-induced involuntary movements occur mainly in the more Parkinson-disabled side (Mones et al., 1971). This suggests that parkinsonism may be critical in determining the presence and the localization of the hyperkinesia (see also Cotzias, 1971). However, no reliable relationship has otherwise been documented between L-Dopa hyperkinesia and Parkinson symptoms.

The purpose of the present study is (1) to compare the localization and the intensity of tardive dyskinesia and L-Dopa-induced hyperkinesia in patients with paralysis agitans, (2) to compare the influence of age on L-Dopa hyperkinesia and tardive dyskinesia, and (3) to relate L-Dopa-induced involuntary movements to the symptoms, localization and severity of Parkinson's disease.

MATERIALS AND METHODS

Subjects. Tardive Dyskinesia. Sixteen psychotic patients with neuroleptic-induced tardive dyskinesia were selected at random among the most pronounced cases of dyskinesia in a total of about 1000 chronic psychiatric in-patients. Age ranged from 37 years to 76 years (median 62). Ten patients were schizophrenic, 6 manic-depressive.

According to our present knowledge, the distribution of tardive dyskinesia is independent of variables such as sex, psychiatric diagnosis and duration of disease (Crane, 1974). No further details of the individual patient data will therefore be given.

Parkinson's Disease. Sixteen patients with both paralysis agitans and L-Dopa-induced hyperkinesia were selected at random from the neurological out-patient clinic. Some characteristics of the patients are shown in Table 1. Patients with disability stages IV – V have an earlier onset of their paralysis agitans (median age 46 years) than patients with disability stages II – III (median age 63 years), the difference being significant ($P < 0.05$, unpaired Wilcoxon test).

There is no significant differences between the two patients groups with respect to age and sex.

All the patients gave informed consent before the study.

Medication. The psychiatric patients had received treatment with various neuroleptic drugs over periods from 1 to 19 years (median 14), while the Parkinson patients had been treated with L-Dopa from $^1/_2$ to 7 years (median 4). In connection with another pharmacological study the patients with tardive dyskinesia were further treated with biperiden (an anticholinergic drug) 12 mg daily for 3 weeks prior to the clinical evaluation. Again, according to our present knowledge, the distribution of the hyperkinetic movements is primarily determined by the individual pathogenetic process in the basal ganglia, independent of the actual neuroleptic given. Furthermore, the treatment with L-Dopa or anticholinergics only uncover or aggravate these topographically predeterminated hyperkinesia. Therefore it is appropriate to compare anticholinergic-aggravated tardive dyskinesia with L-Dopa-induced hyper-

kinesia in Parkinson patients, and therefore these drugs will not be further specified.

Evaluation. In the psychiatric patients the hyperkinesia was recorded twice after treatment with biperiden for 3 weeks. In the Parkinson patients the hyperkinesia was recorded twice during treatment with L-Dopa, while the parkinsonism was rated once after two days without L-Dopa. These two days without L-Dopa were found adequate to provide answers to the problem posed. More prolonged withdrawal was also considered to be unethical.

The hyperkinesia rating scale comprised the 20 most important body segments inolved (see Fig. 1), the degree of hypermotility of each segment being estimated from 0 to 3. The parkinsonism was recorded on the Webster rating scale (Webster, 1968), the symptoms from the right-sided and the left-sided extremities being recorded separately.

The evaluation was supplemented with video-tape recordings.

RESULTS

1. Relationship between Tardive Dyskinesia and L-Dopa-Induced Hyperkinesia. Figure 1 shows the topographic distribution of tardive dyskinesia and L-Dopa hyperkinesia. The tardive dyskinesia is seen to be localized almost exclusively to the oral region, in contrast to the more widely distributed L-Dopa hyperkinesia. The hyperkinesia score for the oral tardive dyskinesia is thus significantly higher than the score for the corresponding L-Dopa hyperkinesia ($P < 0.01$), while the L-Dopa hyperkinesia from the neck (head movements) and the extremities is significantly more pronounced than the corresponding tardive dyskinesia ($P < 0.05$, unpaired Wilcoxon test).

2. Relationship between Hyperkinesia and Age. As shown in Table 1, the oral L-Dopa hyperkinesia in the Parkinson patients was seen more frequently and with increasing intensity with age (Spearman $r_s = 0.77$, $P < 0.01$). The extremity hyperkinesia dominated among the younger patients (Spearman $r_s = 0.65$, $P < 0.05$), although it was also seen in a few of the elderly patients (Table 1). The head movements showed no relationship to age.

In the tardive dyskinesia material, increasing age showed no change in the topographic distribution or in the movement pattern. The oral tardive dyskinesia was only slightly intensified.

3. Relationship between L-Dopa-Induced Hyperkinesia and Parkinsonism. When L-Dopa hyperkinesia was most pronounced, it always dominated in those body segments which in the absence of L-Dopa presented the most pronounced Parkinson symptoms. This was seen most clearly in patients with differing intensity of symptoms in the right and left side or in the upper and lower extremities.

The relationship between the L-Dopa-induced hyperkinetic movements and the main symptoms of Parkinson's disease (without L-Dopa) can be seen

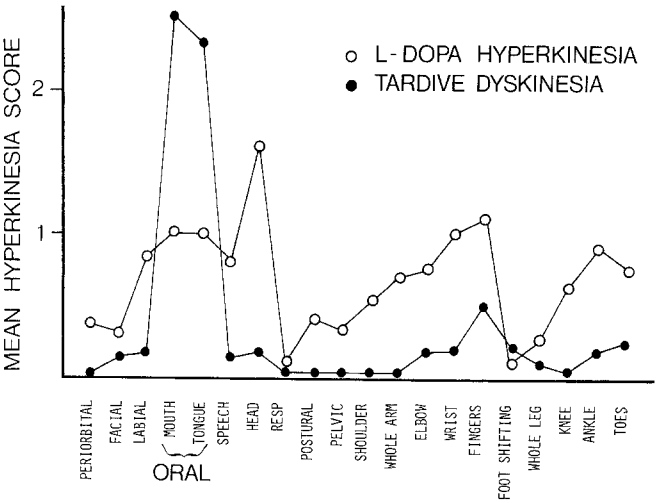

Fig. 1. Distribution and intensity of L-Dopa-induced hyperkinesia ($N = 16$) and neuroleptic-induced tardive dyskinesia ($N = 16$). The degree of hyperkinesia in each region is estimated from 0 (absence of hyperkinesia) to 3 (maximal intensity). There is a significant difference between the two groups with respect to the oral scores ($P < 0.01$), head scores ($P < 0.05$) and extremity scores ($P < 0.05$)

from Table 1. Once the hyperkinesia appeared in the upper extremities ($N = 13$) they were positively correlated to the bradykinesia in the same region (Spearman $r_s = 0.60$, $P < 0.05$). No such correlation could be recorded for rigidity and tremor.

It was characteristic that the hyperkinesia occurred around that fixation point previously associated with bradykinesia and—in most cases—rigidity. For example, if in the untreated state the upper limb was fixed in flexion at the elbow and with pronation of the forearm, then the L-Dopa hyperkinesia presents as flexion and extension on both sides of the original point of fixation and as inward and outward rotation in the long axis of the arm.

Patients with disability stages IV-V were more sensitive to L-Dopa than the patients with disability stages II—III. This was shown by a more pronounced tendency to sudden and rapid fluctuations from hypokinesia to hyperkinesia in relation to the administration of L-Dopa, and by a significantly higher score for the hyperkinesia in the extremities than the patients with disability stages II—III (Table 1, $P < 0.01$, unpaired Wilcoxon test).

Simultaneous occurrence of Parkinson symptoms and hyperkinesia could sometimes be observed during the L-Dopa-induced oscillations from hypo- to hyperkinesia, both with differing localization (in asymmetrical cases with hyperkinesia in the side with the least pre-treatment parkinsonism and with persisting parkinsonism in the other, more Parkinson-disabled side), as well as in the same body segment (for example tremor together with slow writhing movements of

hand and fingers). Simultaneous occurrence of parkinsonism and hyperkinesia was also seen without L-Dopa in patient no. 13, who showed bradykinesia and slight rigidity in the upper limbs, tremor in the lower limbs and a reduced facial expression together with permanent lip smacking. Interestingly enough the latter decreased initially during treatment with L-Dopa to increase later during increased dosage, with rapid tongue protrusion and mouth opening.

DISCUSSION

1. Several neuroanatomical studies in animals have demonstrated the existence of cortico-striatal neuronal fibers connecting every neocortical area with restricted neostriatal regions (Divac, 1968; Künzle, 1975; both with further references). In monkeys, by tracing radioactively-labelled proteins transported by axonal flow, projections from the somatotopic organized motor cortex (mainly area 4) can be followed to the ipsi- and contralateral neostriatum (almost exclusively putamen), where a reversed topographic organization has been found (Künzle, 1975). A topographic arrangement of the efferent striatal fibers including the striato-nigral projections has also been suggested (Voneida, 1960; Szabo, 1962). These data together with some observations of a somatotopic organisation of the basal ganglia in humans (Hassler, 1955; Bernheimer et al., 1973) suggest (1) that in spite of absence of cytoarchitectonic differences, the neostriatum is topically organized, and (2) that using the autoradiographic technique mentioned above it is possible to localize the different somatotopic areas within the neostriatum and possibly other basal ganglia, e.g. the area representing the innervation of tongue and mouth.

The present study has substantiated the clinical impression (Barbeau, 1969) that compared to L-Dopa-induced hyperkinesia in Parkinson patients, tardive dyskinesia almost exclusively involves the oral region. This suggests that the pathological process underlying irreversible tardive dyskinesia (1) is considerably more restricted than the corresponding defect of Parkinson's disease, and (2) is possibly localized to those neurons within the striatum, substantia nigra or other parts of the brain which represent the oral innervation.

2. The observation of a rising tendency to oral preponderance of the L-Dopa-induced hyperkinesia with age, irrespective of the severity of parkinsonism and extra-oral hyperkinesia, suggests a different, independent course of development of the oral and extra-oral hyperkinesia. This emphasizes the necessity to distinguish between hyperkinetic movements in the two regions. The extra-oral hyperkinesia appears to be associated with parkinsonism (see below), while the oral hyperkinesia is apparently more related to age phenomena (possibly parkinsonism in the oral region). The occurrence in older subjects of spontaneous hyperkinesia (senile dyskinesia) (Wiener and Klawans, 1973) involving primarily the oral region, supports this viw.

Consequently, when tardive dyskinesia almost exclusively involves the oral region, it must be reasonable to presume that the irreversible neurotoxic effect of neuroleptic drugs consists mainly of a progression of age-related changes in the oral somatotopic region of the basal ganglia. This should be taken into consideration in future search for the pathogenetic process underlying irreversible tardive dyskinesia.

3. The present study shows that once the L-Dopa hyperkinesia appears *in the extremities*, and the akinesia and rigidity disappear, the hyperkinesia is positively correlated to the localization and the severity of the parkinsonism within the same extremity and more to the bradykinesia than to the rigidity and tremor. This is in agreement with observations of Mones et al. (1971) and suggestions by Cotzias (1971). It should be added, however, that it is an approximate relationship, not a distinct point to point correlation. Both the parkinsonism and hyperkinetic movements might fluctuate to some degree.

This relationship between parkinsonism and hyperkinetic movements supports the hypothesis that hyperkinesia, including tardive dyskinesia, may be determined primarily by a functionally decreased activity of the dopaminergic system, and that the hyperkinetic movement element does not break through until the so-called dopaminergic hypersensitivity develops, or until an anticholinergic treatment has begun. The exact morphological and/or biochemical processes behind these phenomena, including an explanation of the fact that only some but not all L-Dopa-treated Parkinson patients and neuroleptic-treated psychiatric patients develop hyperkinetic movements, remain to be clarified.

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