Parkinsonian symptoms in tardive dyskinesia
A prevalence study

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Summary
Of 49 unselected patients with tardive dyskinesia (TD) 28 (57%) exhibited various parkinsonian signs. Isolated tremor was encountered in 11 patients, tremor with hypokinesia and rigidity in 13 patients, and hypokinesia and rigidity alone in 4. Tremor was detected among patients with scorable peripheral signs of TD. Hypokineto-rigidity, with or without tremor, was attributed to high doses of neuroleptics—notably fluphenazine. This study confirmed reports that isolated parkinsonian signs occurring concurrently with TD must be considered a regular phenomenon even when questionable cases (e.g. tremor in lithium-treated patients, action-tremor in the elderly) are disregarded. However, given the 'fragmentation' of the parkinsonian syndrome, often atypical tremor and signs of anosognosia in TD patients, the final diagnosis may necessitate pharmacological testing (discontinuation of neuroleptic medication, administration of anticholinergics).

Tardive dyskinesia (TD) is believed to result from supersensitivity of dopamine receptors developing in response to a lasting neuroleptic-induced deficiency of dopaminergic neurotransmission. In agreement with this concept, TD typically occurs some time after the symptoms of drug-induced parkinsonism subside, so that the two conditions are seldom encountered together. When they occasionally coexist, there are reciprocal changes of hyperkinesia and parkinsonism during treatment.

However, some investigators have noted parkinsonian symptoms in more than half of their study samples of TD, whereas others have argued that there is a positive correlation between scores of TD and parkinsonism. Given this variance we assessed the prevalence of parkinsonian symptoms in TD during a survey of abnormal involuntary movements in Valkenberg Hospital, Cape Town.

Patients and methods
Patients with abnormal or purposeless movements were selected from four long-term wards for white patients on the basis of personal rounds, or interviews with physicians in charge and nurses. A standardized data sheet was completed for each patient, listing such information as age, handedness, family history, diagnosis and medication. These charts also contained items reflecting information about infections, neurological diseases, brain surgery, traumas, results of laboratory analysis, etc. In addition, a narrative clinical note was read in order to confirm the accuracy of the final diagnosis.

Patients were seen individually. The assessment was conducted in a side room for not less than 10 minutes. During this period questions were asked about complaints, and all movements which had no obvious purpose were noted. The examination format was based on the Rockland scale with modifications.

The parkinsonian score was computed using the scale of Simpson and Angus, modified by inclusion of questions...
examined while the patient was seated in an armchair with the specified (at rest, postural and action). Tremor at rest was scored. In at least a considerable degree of cooperation. The type of tremor was described as typical gait abnormality for the neuropsychological examination of TD.15 The signs of isolated hypokinesia were not scored, as akinetic apathy is not uncommon in chronic institutionalized patients.16 All signs were rated on a two-point (present-absent) scale.

Results

Prevalence

The study sample consisted of 49 patients with scorable symptoms of TD out of 287 patients on chronic medication. Of the 49, 11 exhibited faciolinguai dyskinesia; 1 of these had coexisting parkinsonian symptoms of the hypokinetorigid type such as typical gait abnormality, flexed posture, facial immobility, rigidity and drooling. In 38 patients, in addition to dyskinetic movements in the lower middle facial region, the trunk and/or limbs were involved; this subgroup included 28 (57%) patients with isolated or multiple parkinsonian symptoms. Tremor appeared to be the dominant abnormality perceived as parkinsonian. In 11 patients, tremor at rest was an isolated sign; in 5 of them tremor remained during action. In 13 (26%) patients, tremor at rest occurred together with other symptoms such as flexed posture, facial immobility, loss of arm swinging, gait abnormality; in 3 of these patients, action tremor was also elicited. In 4 (8%) patients there were hypokinetorrigid symptoms in the form of flexed posture, facial immobility, and rigidity, not accompanied by tremor.

Risk variables

Patients with and without parkinsonian symptoms were compared against several variables which are typically considered as contributing to hyperkinesias. Table I summarizes these findings in patients subdivided into groups with four patterns of TD: (i) a group with isolated faciolinguai symptoms (F); (ii) F-group with peripheral signs (FP); (iii) FP with isolated tremor and normal musculan tone (FPT); and (iv) FP with hypokinetorigid symptoms with or without tremor (FPR).

Predictably, the F-group patients had a lower global TD score. The increased TD score in other subgroups was supported by the one-way analysis of variance showing highly significant group effect (F = 9.27; df = 9.27; P < 0.0001). This effect was contributed by the difference between the TD score in the F subgroup and other subgroups (Table I). While the TD score failed to differentiate between the FP, FPT and FPR subgroups, the latter were clearly separable on the basis of the parkinsonian score (F = 14.73; df = 3.45; P = 0.0000). The Bonferroni test indicated that this effect is related to a highly significant difference between FPR and the rest of the subgroups (Table I).

In keeping with observations of mutual antagonism between parkinsonism and TD, a reduced TD score was noted in patients with hypokinesia and rigidity. However, the correlation coefficient computed between the global score of TD and parkinsonism appeared to be weak and non-significant (r=0.14).

Table I demonstrates that sex and organic brain disorder (based on diagnosis rather than on serial psychometric assessment) were not significant factors of either parkinsonism or TD. Only the length of exposure in F-group patients was significantly reduced (P < 0.05) below that in the FP and FPT groups.

Patients with FPT and FPR were on neuroleptics within about the conventional dose range (Table I). When the contribution of individual drugs was assessed separately (dosage disregarded) it appeared that FPR patients were more often prescribed fluphenazine whereas more than 50% of FPT patients were treated with other drugs in addition to neuroleptics. The small size of the subgroups precluded statistical treatment of the data.

Awareness of involuntary movements

While we expected to elicit more complaints in patients with parkinsonian signs, only 2 (both with akathisia) complained of restlessness, tremor and limb movements. The rest of the study sample tended to minimize their peripheral abnormalities and were strikingly oblivious of often grotesque orolinguai dyskinesia despite sometimes incomprehensible speech.

In 4 cases, a decision was made to discontinue antiparkinsonian medication. Within 2 weeks the rigidity increased.

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<thead>
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<th>TABLE I. CHARACTERISTICS OF PATIENT SUBGROUPS WITH DIFFERENT DYSKINESIA PATTERNS AND CONCOMITANT PARKINSONISM</th>
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<td>F (N = 11)</td>
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<td>FP (N = 10)</td>
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<td>FPT (N = 11)</td>
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<td>FPR (N = 17)</td>
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F = faciolinguai dyskinesia; FP = faciolinguai and peripheral signs; FPT = FP subgroup with tremor; FPR = FP subgroup with signs of rigidity with or without tremor; CPZ = chlorpromazine.

* Asterisks denote significantly different values of the Bonferroni test based on the analysis of variance (* P < 0.05; ** P < 0.01; *** P < 0.001) between values marked by vertical lines.

† Continuity (i.e. net) treatment of Craig® would have been a more desirable measure, but it was virtually impossible to restore from available records.

‡ CPZ equivalent units (mg/day) according to Davis and Cole. Fluphenazine was converted on the basis of an equivalent of a 25 mg dose every fortnight to 300 mg CPZ daily.
progressively. All were noticeably annoyed by the recurrence of stiffness and inability to walk and keenly aware of the change.

Discussion

While the prevalence of parkinsonian signs (of about 60%) in the present TD sample was remarkably close to that reported by others,3,6,9 an important concern remained. A number of patients in the present study were on lithium, amitriptyline and phenytoin—drugs known to cause or aggravate tremor.17-20 Lithium-induced tremor, with or without cogwheeling, cannot be considered parkinsonian as it is refractory to anticholinergic medication.21

Also, apart from the parkinsonian-type tremor at rest, there were cases of postural and action tremor. The existence of the latter subtypes in the same patient does not rule out the presence of idiopathic or drug-induced parkinsonism.22 Moreover, Jeste and Wyatt2 argue that neuroleptics more often induce postural or action tremor than tremor at rest. However, when the age of patients was analysed, it appeared that individuals with only tremor at rest are significantly younger than those who in addition have a stable action tremor (59.8 ± 14.4 v. 74.0 ± 9.1 years; P < 0.05, Student's t-test, two-tailed). Assuming that in some cases action tremor of the elderly and of patients on lithium therapy may not represent true parkinsonian signs, we arrive at a prevalence of about 40%. While this change may be perceived as a cosmetic improvement, even this figure can be challenged. Parkinsonism occurring concomitantly with TD was so modified (‘fragmented’) that it was seldom (in 34%) seen in the form of the syndrome and the final diagnosis of the condition may require pharmacological testing.

To illustrate the point further, one should add that unlike patients with parkinsonism who often present with different symptoms of depression23 only 2 patients with TD (and akathisia) in the present sample (4%) complained of subjective tension and were distressed by their motor incapacity. The rest tended to minimize abnormalities of locomotion or were oblivious of other grotesque orolingual movements. Why patients with TD should develop signs of ‘anosognosia’ is not immediately apparent. A number of investigators,10-12,14-16,18-20 have written on the subject but the nature of this perplexing phenomenon remains enigmatic. It should be recalled that patients with idiopathic parkinsonism predominantly affected by tremor, which is considered a transitional symptom between parkinsonism and hyperkinesia,7 feel subjectively better than individuals with hypokinesia as a predominant sign.23 We elicited bitter complaints of stiffness and inability to walk from TD patients within about 2 weeks of cessation of anticholinergic medication. Similarly, individuals treated with L-dopa are reported to be better able to tolerate and even prefer complications in the form of severe dystonic and choreiform hyperkinesias to being hypokinetically.12,17 Duvoisin2 remarks that a patient’s preference may be a useful guide to dosage in cases of poor response to long-term L-dopa treatment. Considering that TD and L-dopa-induced dyskinesia represent a single entity28 we believe that this recommendation must be considered in weighing the benefit-to-risk ratio in therapeutic solutions of the TD-parkinsonism dilemma.

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REFERENCES