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Tardive Dyskinesia

Haag WHO TD eyeblinking

Published on behalf of the World Health Organization by

Hogrefe & Huber Publishers

Seattle · Toronto · Bern · Göttingen

1992

Table 1. Classic tardive dyskinesia.

General characteristics

- often resembling normal (chewing, licking, grasping) or repetitive choreic movements
- monotonously repeated with a low frequency of about 10–40 min^{-1}
- involuntary, can often only temporarily be suppressed by volition; patients often unaware of dyskinesias.
- activation by voluntary movements of non-affected muscle groups
- lack of a subjective feeling of inner restlessness
- reduced with drowsiness or sedation, absent during sleep

Individual symptoms

Face

- tongue: protrusion, "bonbon sign", vermicular contraction
- jaw: vertical or horizontal chewing movements
- perioral: pouting, "bridling"
- others: distortion of the eyebrows, frowning, eye-blinking

Extremities

- fingers: "piano-playing" movements, grasping
- wrists: rotatory and flexion/extension movements
- toes: flexion/extension movements
- ankles: rotatory and flexion/extension movements
- legs: stamping movements

Trunk

- hip-rocking
- irregular contractions of diaphragm (grunting, respiratory difficulties)
- others: head nodding, shrugging of shoulders, rocking movements of the upper torso

tients perform these movements involuntarily, and – with more severe forms of the disorder – they are at best temporarily capable of suppressing these involuntary movements. There is often a striking discrepancy between the objective motor restlessness and the lack of a subjective feeling of inner restlessness. Many patients with tardive dyskinesia do not even notice their involuntary movements unless their attention is drawn to them by other persons. Sixty percent of the 138 tardive dyskinesia patients in our own epidemiological survey (HAAG et al., 1985) maintained they had not yet noticed their abnormal movements, and only 33% experienced mild or moderate distress.

Table 2. Tardive dystonia.

General characteristics

- resembling dystonia musculorum deformans
- sustained dystonic contractions that may lead to muscular hypertrophy or fixed postures
- involuntary, can often only temporarily be suppressed by volitional effort
- in some patients brought out by volitional action of affected muscle groups ("action dystonia")
- lack of a subjective feeling of inner restlessness
- decreased with drowsiness or sedation, absent during sleep
- patients usually aware of, high subjective discomfort

Individual symptoms

Face

- tongue: sustained tonic protrusion
- jaw: sustained tonic opening of the mouth
- eyes: blepharospasm

Extremities

- legs: inversion, plantar flexion of the feet, "spastic" gait
- arms: abduction of the shoulder, flexion of the elbow, hyperextension of wrist and fingers

Trunk

- torticollis, retrocollis
- shoulder and pelvic girdle: twisting and undulating movements
- axial dystonia, lateral flexion of the spine

neck. Tardive dystonia does not exhibit such a clear-cut periodicity as classic tardive dyskinesia; thus, frequency counts are not useful as an indicator of severity.

In some patients dystonic contractions are activated only when voluntary movements of the respective muscle groups are performed. This phenomenon has been referred to as *action dystonia* by some authors.

Interestingly, dystonias may be brought about only by slow movements or other specific movement patterns. For example, the attempt to walk slowly or at normal speed may result in intensive dystonic contractions, making walking virtually impossible. Yet the same patient may have surprisingly little difficulty running, climbing up chairs or riding a bike.

Some patients with idiopathic torticollis spasmodicus manage to control their dystonic contractions by slightly pressing their hand against the cheek ("geste antagoniste"). Similarly, some patients with tardive dys-

Table 8. Psychosocial and physical impairment by tardive dyskinesia.

Psychosocial
– feeling of embarrassment and guilt; shame; depression; social withdrawal
– handicapped in personal relationships, stigmatization by strikingly abnormal movements
– difficulty in professional activities
Physical
– denture problems, ulceration of the tongue, difficulty in swallowing
– dysarthria, spastic dysphonia
– respiratory disturbances
– gastrointestinal disturbances
– difficulty in motor function (fine motor skills, walking etc.); falls and injuries
– fixed postures
– increased mortality?

reported statistical association of tardive dyskinesia with increased mortality would be a direct causal connection (e.g. from an increased incidence of deaths by choking). Another possibility – and probably the more important one – is the existence of a common variable predisposing to both, tardive dyskinesia and increased mortality.

THE NATURAL COURSE OF TARDIVE DYSKINESIA

Initially, it was believed that tardive dyskinesia develops only after a minimum period of two or more years of continued neuroleptic exposure. But there is only little empirical evidence supporting the idea of such a minimum threshold for tardive dyskinesia development. In a prospective study, KANE and colleagues (1984) showed that the yearly incidence of tardive dyskinesia stayed fairly constant for the first seven years of treatment. There are case reports of an occurrence of tardive dyskinesia after as little as three months and sometimes after even shorter courses of treatment (CHOUINARD & JONES, 1979).

The study by KANE et al. cited above suggests that there may be important differences between cases with an early onset (less than two years of neuroleptic treatment) and cases with a later onset (after more than two years), since early-onset tardive dyskinesia was found to be associated with significantly lower maximum neuroleptic doses than late-onset tardive dyskinesia. This might indicate that early onset of

Table 9. Signs preceeding the onset of tardive dyskinesia.

– tongue fibrillation; minimal choreoathetoid movements of the tongue when extended by the patient
– minimal perioral choreoathetoid movements
– increased frequency of eye-blinking
– eyelid and tongue tremor
– "marching syndrome": walking in place like soldiers marking time (with or without a feeling of subjective restlessness)?
– tardive akathisia?
– muscular hypotonia?

tardive dyskinesia is more closely related to an increased individual vulnerability rather than to the intensity of neuroleptic therapy.

Tardive dyskinesia usually has an insidious onset, and the date of first appearance can often not be determined precisely in retrospect. For an early diagnosis of tardive dyskinesia it would be of great interest to know the very first clinical symptoms. Some (listed in Table 9) have been suggested as early signs of tardive dyskinesia. However, these are only tentative and need to be corroborated in prospective studies (GARDOS et al., 1983 a).

The clinical manifestation of tardive dyskinesia is often precipitated by a dose reduction or withdrawal of neuroleptics, or by concomitant administration of anticholinergic drugs (antiparkinsonian drugs, some antidepressants).

Once the symptomatology of tardive dyskinesia has fully developed, a rapidly deteriorating course is very uncommon, and – if present – should rise doubts whether the diagnosis is in fact correct.

If neuroleptic drugs can be withdrawn completely, tardive dyskinesia remains either stable or slowly improves with time (except for an initial transient rebound aggravation caused by the "unmasking" effect of neuroleptic withdrawal). In general, the rate of improvement appears to be highest during the first months after discontinuation of neuroleptics. However, it should be pointed out that full remissions may occur as late as two to five years after withdrawal.

Table 10 shows several studies investigating the reversibility of tardive dyskinesia after neuroleptic withdrawal. Most of these studies were performed on older, chronically institutionalized populations, so that the unfavorable results obtained cannot be generalized. Studies involving younger patient samples (YAGI et al., 1976, QUITKIN et al., 1977) have reported considerably higher rates of remission (53% and 92%, respectively).

Table 10. Remission of tardive dyskinesia after withdrawal of neuroleptics.

Author	Follow-up Period (months)	TD-Patients n	remitted (%)	improved (%)
Paulson (1968)	3	33	0	–
Degkwitz (1969)	7–10	273	19	19
Edwards (1970)	12	19	5	–
Crane (1971)	6–24	39	8	–
Hershon et al (1972)	4	23	0	–
Yagi et al. (1976)	12–24	19	53	–
Quitkin et. al. (1977)	1–24	12	92	–
Jeste et al. (1979)	7	21	57	–
Glazer et al. (1984)	1–27	33	3	24

Overall, recent studies have led to the more optimistic appraisal that tardive dyskinesia is by no means irreversible in all instances, though irreversible cases do occur (CRANE, 1973). It is probably fair to assume that, on the average, tardive dyskinesia fully remits in about half of the patients once neuroleptics have been discontinued.

Neuroleptic withdrawal is desirable; however, a large number of patients require continued antipsychotic medication. Several studies on the course of tardive dyskinesia with continued neuroleptic treatment have yielded inconclusive results (BERGEN et al., 1989). Though increased dosages of neuroleptics can temporarily suppress the symptoms of tardive dyskinesia, they are likely to further aggravate the underlying pathology. Several studies reported a deterioration of tardive dyskinesia under continued neuroleptic medication or reserpine (KAZAMATSURI et al., 1972). Moreover, and perhaps of greater significance, the reversibility of tardive dyskinesia appears to decrease with continued exposure (JESTE et al., 1979).

With repeated administration of neuroleptics, there may be a gradual shift from transient dyskinesias (present only for up to three months) to more persistent and perhaps irreversible forms of tardive dyskinesia. In an interesting study using the primate model of tardive dyskinesia (KOVACIC & DOMINO, 1982), neuroleptic treatment was repeatedly stopped in a dyskinetic monkey until the complete disappearance of clinical symptoms. Then, neuroleptic treatment was recommenced. The persistence of dyskinesias after each treatment cycle increased progressively, suggesting that – despite of the lack of visible dyskinesias at the end of the drug-free intervals – some underlying pathology had persisted to be further aggravated by renewed exposure to neuroleptics.

The relationship of dyskinesias following abrupt withdrawal of neuroleptics and tardive dyskinesia remains unclear. These "withdrawal dyskinesias" (sometimes referred to as "withdrawal emergent syndrome") are usually self-limited and remit spontaneously after several days or weeks. However, persistent forms of tardive dyskinesia may also make their first appearance after discontinuation of medication. Thus, "withdrawal dyskinesias" may represent the endpoint of a continuum (from very short-lasting to irreversible dyskinesias) rather than a distinct entity.

The issue of reversibility of tardive dyskinesia is further complicated by the fact that some patients (on stable neuroleptic doses) exhibit pronounced spontaneous fluctuations in the severity of tardive dyskinesia. In some instances an intermittent course of tardive dyskinesia over a period of years was observed (JESTE & WYATT, 1982b; own observations). "State-dependent" dyskinesias have been described in several case reports: There is an increase in severity during or even preceding depressive episodes and a decrease in severity during mania, these fluctuations not being attributable to changes in medication (CUTLER & POST, 1982).

In view of this one might even speculate that rarely do dyskinesias become clinically apparent for the first time after extended periods without neuroleptic medication. Even in those cases with an onset of dyskinesia years after discontinuation of neuroleptics, previous neuroleptic medication may be considered as a contributing factor in the etiology of the disorder.

TARDIVE DYSKINESIA AND "TARDIVE DYSMENTIA"

There have been speculations on a possible deteriorating effect of long-term neuroleptic treatment on the mental status of patients paralleling the development of tardive dyskinesia. WILSON et al. (1983) found a significant positive correlation between severity scores of tardive dyskinesia and some variables regarded as indicators of dementia (e.g. loud speech, unstable mood). The authors interpreted their findings as supporting the notion of a neuroleptic-induced "tardive dysmentia." Findings of mild abnormalities in cranial computer tomography and of poor performances in psychological testing in patients with tardive dyskinesia have also been interpreted by some as resulting from long-term neuroleptic toxicity (FAMUYIWA et al., 1979). However, these abnormalities are more likely factors predisposing to the development of