

TARDIVE DYSKINESIA

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Tardive dyskinesia is defined as a disorder of involuntary movements that appears after at least 3 months of treatment with neuroleptic drugs and is not attributable to some alternative causes (1). It was first described in 1957 as orofacial dyskinesia, and later as bucco-linguo-masticatory dyskinesia. A review of 19 papers by Crane (1973) (2) of more than 20,000 patients showed a prevalence of between 0.5% and 39%. The difference in rate is partly due to the differences in methodology, patient populations, and definitions of the syndrome which vary from mild and transient to severe and persistent cases. Kane and Smith (1982) (3) reported its prevalence on 56 samples of 35,000 neuroleptic-treated patients as 20%. Gerlach and Casey (1988)(4) believed that the rate for irreversible cases was lower. Omitting the spontaneous cases (5%) and reversible cases (12%) they reduced the prevalence to 3-6%.

The original description of tardive dyskinesia referred to the classic bucco-lingual-masticatory triad. This consisted of involuntary movement of the lips, licking and sudden protrusion of the tongue, and chewing movement of the lower jaw. The earliest sign was abnormal tongue movements. Later descriptions included other abnormal movements like facial grimaces, blinking, pouting, smacking of the lips, the "bonbon" sign (pressing tongue against the cheek muscles), choreoathetoid movements of the fingers, hands, arms and feet, ballistic movements of arms, axial hyperkinesias and diaphragmatic movements causing grunting, speech defects and akathisia (5).

The diagnosis of tardive dyskinesia will require a period of neuroleptic treatment (at least 3 months) and it will be further reinforced if the symptoms can be reduced by increasing the dose or become more severe on reducing or withdrawing the neuroleptic (1).

DIFFERENTIAL DIAGNOSIS

Tardive dyskinesia usually begins after 1-2 years of continual neuroleptic treatment. It must be differentiated from other movement disorders like multiple tics,

Gilles de la Tourette's syndrome, Parkinsonism, akathisia, the rabbit syndrome, mannerisms and stereotyped motor behaviour of psychotic patients, senile dyskinesia, Huntington's chorea, Wilson's disease, torsion dystonia and movements disorders resulting from brain damage, metabolic disorders and drug intoxication.

CLASSIFICATION

Tardive dyskinesia can be classified according to its severity and chronicity, into at least three types (1):

1. withdrawal tardive dyskinesia
2. transient tardive dyskinesia
3. persistent tardive dyskinesia

It can also be classified according to its clinical manifestations into 4 types (6):

1. withdrawal emergent syndrome which is characterized by choreic movements and usually appears in children lasting 6-12 months;
2. tardive dystonia which resembles torsion dystonia and usually affects children and tends to be persistent;
3. tardive akathisia where the onset is later and the akathisia is made worse by withdrawal of neuroleptics;
4. classical tardive dyskinesia which appears to belong to two subgroups characterized by: (a) bucco-lingual-masticatory movements, and (b) abnormal movements in other parts of the body.

Except for classical tardive dyskinesia, the other subtypes are less commonly reported. The three cases reported by Chiu et al (1989) (7) showed that the condition may not be that uncommon. Tardive dystonia is slightly different from classical tardive dyskinesia in that it tends to affect males and younger patients, and more resistant to drug treatment, but it may be treated with anticholinergic drugs, as illustrated in the three cases reported by Chiu et al (1989).

NEUROPATHOPHYSIOLOGY

It is generally accepted that tardive dyskinesia (which includes tardive dystonia) is due to super-sensitivity of dopamine receptors resulting from prolonged neuroleptic administration. Withdrawal of neuroleptics often causes emergent tardive dyskinesia (withdrawal dyskinesia) or exacerbation of dyskinesic movements in established cases. The dyskinesic movements can also be reduced by dopamine D2 blockers such as sulpiride and oxiperomide (4). Recent observations cast doubts on this theory because animals developed dopamine hypersensitivity rapidly (often after a single injection of neuroleptic) while tardive dyskinesia developed only

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after at least a few months. There was no increase in dopamine-mediated endocrine functions and no increase in dopamine receptors in the postmortem brains of tardive dyskinesia patients. An alternate GABA hypothesis was postulated by Gunne L M et al (1984) (8).

TREATMENT

There is no single satisfactory treatment for tardive dyskinesia. The main treatment is prophylaxis. Psychiatrists should be made more aware of the condition, its early diagnosis and the risk factors with the aim to prevent its development.

This could be achieved by:

- (1) proper selection of antipsychotic drugs eg. low potency drugs like thioridazine, pimozide, sulpiride, clozapine;
- (2) supplementing antipsychotic treatment with lithium, benzodiazepines or carbamazepine for high risk groups eg. the aged, females, and presence of organic factors like alcoholism;
- (3) avoiding acute extrapyramidal side-effects (acute dystonia, parkinsonism, akathisia), as these early syndromes are associated with tardive dyskinesia;
- (4) reducing the antipsychotic drugs to a minimal effective dose and avoiding high doses and drug holidays (more than one week);
- (5) slow reduction (one third of total dose per month) when antipsychotic medication can be withdrawn;
- (6) reduction and withdrawal of anticholinergic (anti-parkinsonian) drugs early;
- (7) periodic (3 monthly) reviews for early signs including a trial period of drug withdrawal (less than one week);
- (8) stopping the offending drugs as soon as tardive dyskinesia (or tardive dystonia) is detected;
- (9) informing the patient (and relatives) about the condition and the choice of subsequent treatment (as a medico-legal precaution).

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Specific drug treatment has not been found to be satisfactory. Dopamine blockers like thioridazine, haloperidol, pimozide, sulpiride and oxiperomide, can be used to produce immediate and temporary suppression of symptoms. This apparent improvement will be followed by a more severe tardive dyskinesia unresponsive to other therapies. Dopamine-depleting agents like tetrabenazine up to 200 mg daily in divided doses were used in past regimes. Side effects were hypotension, parkinsonism, drowsiness, confusion and depression (9). Agents that preferentially block the dopamine D2 (non-adenylate cyclase-linked) receptors have been found to decrease tardive dyskinesia. These were metoclopramide, tiapride, sulpiride, oxiperomide and remoxipride. Recent studies showed that tiapride 200-400 mg/day (10), oxiperomide 10-40 mg/day (11) and remoxipride 150-600 mg/day (12) reduced involuntary movements.

As a reciprocal antagonism exists between striatal dopaminergic and cholinergic systems, those agents that increase acetylcholine activity also relieve tardive dyskinesia. Physostigmine i/v up to 1-2 mg (13) and deanol up to 1600 mg/day (14) was found to decrease tardive dyskinesia. GABAergic drugs like baclofen (beta-p-chlorophenyl-GABA) and sodium valproate which inhibits GABA transaminase were found to be effective. Other drugs found to benefit some patients include propranolol (beta-adrenergic blocker), clonidine (alpha2 adrenergic receptor agonist), alpha-methyldopa (a "false transmitter"), neuropeptides like met-enkephalin and ceruletide, lithium, and vitamin E (alpha-tocopherol). Vitamin E up to 1200 IU/day was reported to improve tardive dyskinesia. This is attributed to the free radical scavenging action of vitamin E (15).

Tardive dyskinesia, which includes tardive dystonia, is a serious long term side-effect of antipsychotic medication. As it responds poorly to treatment, special attention must be paid to its detection and prevention.