TARDIVE DYSKINESIA I: CLINICAL AND BIOCHEMICAL ASPECTS

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Tardive dyskinesia is a late side-effect of chronic neuroleptic therapy and is one of a number of disorders of movement secondary to dysfunction in the basal ganglia. The dyskinesias most commonly seen in neurological practice comprise a number of clinical conditions characterised by the spontaneous development of abnormal movements, they include *tremor*, which is manifest as a rythmic, sinusoidal movement, *chorea*, manifest as recurrent random continuous brief muscular contractions, *myoclonus*, characterised by repetitive discrete muscle jerks, and *torsion dystonia*, with sustained muscle spasm leading to grotesque posturing.

These movement disorders can be caused by disease or can be secondary to the effects of drugs; in many cases disease of the basal ganglia or side-effects of drugs which exert potent pharmacological actions

since then increased awareness could ac- on the basal ganglia are known to contribute significantly to the aetology.

Neuroleptics are used widely in the treatment of schizophrenia and are well known to produce a Parkinsonian syndrome characterised by akinesia, rigidity and tremor with occasional dystonia. What is perhaps less widely known is that, whereas Parkinsonian side-effects occur early in treatment, respond to anticholinergic drugs and can disappear spontaneously, the syndrome known as tardive dyskinesia occurs late in therapy, is aggravated by anticholinergic drugs and could be irreversible.

The clinical syndrome was first described by Sigwald et al (1959) and has been comprehensively studied (Klawans 1973, Brandon et al 1971, Crane 1968. Turek et al 1972). It occurs predominantly in patients over 40 years of age with a history of prolonged neuroleptic therapy and is seen more commonly in females than in males. The disorder is characterised clinically by-involuntary, grotesque movements of the tongue and peri-oral musculature which are often socially objectionable and which could prove to be a source of considerable embarrassment. The movements disappear during sleep, worsen under stress and a measure of limited voluntary control is possible. Symptoms can be precipitated by a reduction in dosage of phenothiazine or appear after the drug has been withdrawn. The dyskinetic movements can generalise to the trunk and limbs and complications include hypertrophy of the tongue, ulceration of the mouth, dysphagia with subsequent malnutrition, dysarthria, and loss of balance.

Incidence

There has been considerable disagreement about the frequency of drug-induced tardive dyskinesia. The syndrome was not reported regularly until after 1964 and since then increased awareness could account for an apparent increase in frequency; furthermore spontaneous dyskinesias can occur in 16% of a chronic geriatric hospital population and this further complicates the assessment of frequency. Surveys have therefore shown a wide range of incidence from 5% (Kline 1968) to 36% (Fann et al 1972) of a chronic psychiatric in-patient population, with females outnumbering males in a ratio of 2:1. Most studies suggest an incidence of about 25% of chronic psychiatric in-patients over 50 years of age. Kline (1968) has suggested that the incidence of 'true' tardive dyskinesia is minimal as most patients said to be effected had concomitant brain damage, and has warned against the dangers of precipitating "a nonexistent epidemic of a rare side-effect".

Predisposing Factors:

1) Chronic phenothiazine therapy has been shown to be associated with the subsequent onset of tardive dyskinesia — the syndrome was rarely seen in Turkey where phenothiazine drugs are used sparingly. While simple dyskinesias can occur spontaneously in the elderly, complex dyskinesias are unlikely to be due to simple deterioration due to age. Among the phenothiazines, those known to induce extrapyramidal side-effects more readily early in treatment are also more likely to predispose to tardive dyskinesia; all drugs producing dopamine blockade predispose to tardive dyskinesia but the piperazine group of phenothiazines are more often implicated. In patients over 55 years of age the risk of dyskinesia rises if phenothiazines are given in doses of 200 mg/day or more for six months or longer.

2) Duration of therapy — although tardive dyskinesia is a late side-effect of therapy, a statistically significant relationship between the duration of therapy and the incidence of the syndrome has yet to be shown. A relationship has been shown however between the total drug intake and the subsequent development of tardive dyskinesia. The minimum amount of neuroleptic required to produce oral dyskinesia was 14g and the minimum duration was seven months (Crane and Smeets 1974).

3) Brain damage — this has been associated with the emergence of tardive dyskinesia; while brain damage can arise as a result of a number of causes, including senility, degenerate disease and alcoholism, 52% of patients with tardive dyskinesa did not show clinical evidence of brain damage. An organic brain syndrome is particularly likely to accompany the disorder in patients under 50 years of age (Brandon et al 1971), and Edwards (1970 has shown a significantly higher incidence of brain damage in a group of elderly female patients with persistent oral dyskinesia than in controls. Post-mortem studies have been inconclusive; Hunter et al (1968) could find no specific lesion to account for the syndrome whereas Faurbye and Christensen (1967) showed cortical gliosis in all their 28 patients, degeneration in the substantia nigra in all but one, and gliosis of the brain stem and mid-brain in 25 patients, Marshall (1972) has shown cell degeneration in brains of 27 of 28 adults with tardive dyskinesia.
4) Genetic and constitutional factors: females outnumber males by a factor of two to one and this could suggest a constitutional predisposition to the disorder or possible sex differences in the mode of metabolism of neuroleptics with the preferential formation in females of metabolites which could predispose to tardive dyskinesia. A survey by Crane (1974) showed however that the reported greater sensitivity in females could be attributed to the fact that more older women could be found in a hospital population. Others have suggested the possibility of an additional endogenous allergic factor (Yonchev et al 1972). Brandon et al (1971) noted a preponderance of blue-eyed males in their sample which suggested a genetic predisposition to oral dyskinesia in these patients.
5) Anticholinergic drugs: these are widely prescribed in the control of early extrapyramidal side-effects of neuroleptics. They are known to elicit choreiform movements in patients with oral dyskinesia in the later stages of treatment and also in the patients with Huntington's chorea (Kalwans and Rubowitz 1974), but they do not produce such movements in normals. There is also some evidence to suggest the incidence of tardive dykinesia is greater in patients receiving a neuroleptic with an anticholinergic drug than in patients receiving a neuroleptic drug alone; indeed, while anticholinergic drugs may mask Parkinsonian side-effects, they may increase the intensity and duration of dyskinetic symptoms and could lower the threshold for the manifestation of tardive dyskinesia.

Biochemical and Pharmacological Aspects

Facial dyskinesias are a common side-effect in patients treated with drugs, such as L-Dopa, known to enhance the activity of dopaminergic systems, and Korczyn (1972) has proposed that these dyskinesias are due to increased levels of dopamine at receptor sites in the caudate nucleus. Phenothiazines and other neuroleptics block dopamine receptors in the brain and this blockade produces a Parkinsonian syndrome in some patients during the early part of treatment which may persist throughout treatment or subside. The cause of tardive dyskinesia is not clear, it may be associated with prolonged changes in central dopamine mechanisms and it could be related to the development of dopamine receptor hypersensitivity upon chronic blockade by the drug. Dopamine receptor blockade in the striatum is equivalent to a chemical denervation of dopamine sensitive cells; if phenothiazine therapy is prolonged this may lead to a denervation hypersensitivity in these cells which will then respond abnormally to the presentation of dopamine at receptor sites. A reduction in dosage of neuroleptic, or drug withdrawal, or even altered metabolism of the drug, might lead to more dopamine leaking through and reaching hypersensitive receptors. This would account for the appearance of abnormal movements in some patients when dosage is reduced or when the drug is withdrawn.

Treatment with a dopamine precursor, such as L-Dopa, or a dopamine receptor agonist, such as amphetamine, apomorphine, or bromo-ergocryptine, all lead to increased dopamine receptor activity and could therefore be expected to make the symptoms of tardive dyskinesia more marked; this has in fact been repeatedly shown to be the case.

An animal model for dopamine receptor hypersensitivity following striatal denervation by 6-hydroxydopamine (Ungerstedt 1971) or by receptor blockade with drugs (Moore and Thornburg 1975) has been described, and Klawans and Rubowits (1972) have proposed that increased sensitivity in guinea pigs to dopamine agonists induced by chronic chlorpromazine therapy could be analagous to tardive dyskinesia.

Cholinergic mechanisms are also involved; there is likely to be a crucial balance between dopaminergic and cholinergic mechanisms in the striatum and manipulation of one or other of these could alter the symptoms arising from dysfunction in the other. It is well known that physostygmine, a cholinergic drug, alleviates symptoms in Huntington's chorea, probably by increasing the availability of acetylcholine to counteract the dopaminergic hyperactivity presumed to underline the hyperkinesis.

Kalawns and Rubowits (1974) have suggested that tardive dyskinesia represents an imbalance between dopaminergic and cholinergic systems in the striatum due to dopamine receptor hypersensitivity, and that symptoms would be relieved by a cholinergic drug and worsened by an anticholinergic drug. They showed that physostygmine led to an improvement in motor symptoms within 5 minutes of intravenous administration while scopolamine led to a deterioration lasting for up to three hours. Anticholinergic drugs could therefore further accentuate the imbalance between striatal dopaminergic and cholinergic mechanisms and may be instrumental in precipitating symptoms in patients in whom the syndrome might otherwise have remained subclinical.

The role of cholinergic mechanisms in tardive dyskinesia would provide strong evidence against the routine prescription of anticholinergic drugs in patients being treated with neuroleptics, and strong reasons for a periodic review of the requirements for anti-parkinsonian medication during maintenance therapy. The paucity of knowledge about the pharmacokinetic and pharmacodynamic effects of many commonly used neuroleptics, together with the high incidence of inter-individual differences in absorption, metabolism and clinical response, would in fact suggest that careful manipulation of the dose of phenothiazine administered should be the first line of action against extrapyramidal side effects and that anticholinergic drugs could be used more sparingly.

Serotonergic mechanisms could also be implicated but there is no information on the influence of serotonergic or antiserotonergic drugs on the syndrome.

Outcome

The persistence of dyskinesia in spite of attempts at treatment in some patients has led to tardive dyskinesia being described as 'a terminal insufficiency syndrome' or as 'an epiphenomenon of neuroleptic therapy'. The irreversibility of some symptoms in a high percentage of cases, although disputed by Kline (1968), has been one of the major causes of the renewed and growing intrest in this condition. There has been no consistent effect shown following changes in phenothiazine regimes once the syndrome appeared, though it has been noted that patients with tardive dyskinesia who are maintained on small doses of neuroleptics do not show any increase in symptomatology (Crane 1973). Outcome has also been related to severity of symptoms, and patients with limited symptoms have been shown to be more likely to become symptom free than patients with more severe symptoms. Although some drugs provide symptomatic relief the long term outcome remains obscure.

Tardive dyskinesia remains a sober reminder of the constant need to rationalise neuroleptic drug therapy and to monitor both therapeutic and unwanted effects

It is one of the more disabling and grotesque forms of iatrogenic disease and it adds to the evidence that medicine may still have to learn from "..... the tragic lesson of the past, namely that the manifestation of 'schizophrenic' psychoses can only be reduced somatotherapeutically by agents which damage the brain, (which) can be traced in an unbroken progression from the gyrating chair in the nineteenth century, through insulin coma, electroconvlusive therapy and leucotomy, to modern neuroleptic drugs". (Haddenbrock 1964).

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