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Cognitive Dysfunction and Tardive Dyskinesia

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Summary: From a prospective study of tardive dyskinesia (TD), psychiatric patients with neuroleptically—induced "persistent" TD were contrasted with controls on a neuropsychological measure of abstracting ability. A significant association is demonstrated between impaired cognitive performance and TD, even when the neuropsychological measure was obtained in advance of TD onset.

Tardive dyskinesia (TD) continues to generate clinical concern among practitioners and investigators involved in the pharmacological management of major psychiatric disease (Tarsy and Baldessarini, 1976; Crane and Smith, 1980; Baldessarini *et al,* 1980). Variables denoting risk for TD are poorly understood and this iatrogenic disorder continues to constitute an unpredictable clinical event. Jeste and Wyatt (1982) have produced an especially comprehensive and useful volume on the issue.

Although numerous variables have been examined in relation to its development, psychometric or neuropsychological test measures have received only scant attention as possible correlates or precursors. The few studies using such measures have either been unable to demonstrate empirical relationships between psychological test results and clinical TD (Asnis *et al,* 1977; Famuyiwa *et al,* 1979; Jose *et al,* 1979; Kane *et al,* 1981) or have produced sharply conflicting results (Edwards, 1970; Pryce and Edwards, 1966).

Our own studies of cognitive dysfunction in TD have employed the Conceptual Level Analogy Test (CLAT) developed by Willner (1970, 1971). This instrument consists of 42 multiple choice analogy items graded to assess conceptual functioning, ranging from simple to quite complex. Furthermore, all analogy items were experimentally screened using a method described elsewhere (Willner, 1964) to ensure that they could not be solved by word association. The CLAT also controls for excessive vocabulary and information level by using items understandable by the average fourth grade student. We wondered if the CLAT would be useful as a neuropsychological variable in the study of neuroleptically induced TD. Initially we reviewed the first 300 patients admitted to a large prospective study of TD run by one of the authors (FAS), and identified 184 subjects who had adequate CLAT testing at or prior to study entrance, and who were being treated with anti-psychotic medications. When CLAT scores were contrasted with those on the Simpson Dyskinesia Scale (Simpson *et al,* 1979) a significant association was found (Struve *et al,* 1982). This association was especially robust for subjects with longer drug exposure.

While offering considerable indirect encouragement, the above findings did not directly address the issue of TD as a diagnosed clinical syndrome. This was because the dependent measure involved only the number of positive symptoms on the Simpson Dyskinesia Scale without regard for overall clinical diagnostic impression. In this present report our current findings suggest that a strong empirical association may exist between cognitive dysfunction as measured by impaired CLAT performance and the diagnosed clinical syndrome of persistent TD itself. Furthermore, the findings of cognitive impairment may preceed in time the onset of TD.

Method

The subjects consisted of those psychiatric patients participating in a long term prospective study of TD who either (a) already displayed presumptive clinical TD at study entry (baseline TD) or (b) developed presumptive clinical TD sometime during subsequent follow-up (prospective TD). They were detected by trained examiners using a modification of the Simpson Dyskinesia Scale which allows global judgements of clinical TD. Diagnostic assessments were made without knowledge of CLAT scores or other prodromal variables under investigation. Baseline TD involved a global rating of at least mild TD made by one examiner. Criteria for prospective TD were more stringent and required that three examiners all provide independently and without cross communication a global rating of at least mild TD. Of 103 TD subjects thus found, 23 were omitted because cognitive testing (CLAT) had not been done. For the remaining 80 TD subjects the longitudinal clinical course following

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initial TD documentation was examined. Seventeen patients were found to display either transient dyskinesia or withdrawal dyskinesia using criteria suggested elsewhere (Schooler and Kane, 1982) and were omitted as well. In both transient and withdrawal TD, the TD is remitting within three months and this is not related to reinstatement of or increase in neuroleptic dose. Withdrawal dyskinesia first becomes manifest following neuroleptic discontinuation. An additional nine subjects had to be dropped because inadequate follow-up did not permit categorization of the TD as either persistent or nonpersistent. Of the 54 patients with persistent TD, the three oldest subjects (ages 64, 67, 68) had to be omitted to allow age comparability with the control group. All three subjects had impaired CLAT performance and thus their omission operated against our hypothesis.

Selecting a control group in TD research is always methodologically awkward. Since TD becomes manifest over time one can never be certain that a given patient will not develop it. Even when TD and non-TD groups are matched closely on numerous variables (age, sex, neuroleptic exposure, etc.) it remains likely that an unknown portion of one's control group may subsequently develop the syndrome. Our solution was to select control subjects not based on traditional matching approaches but rather based instead upon such subjects meeting the far more stringent criteria of survival without TD for a period of five years, the period of exposure to drugs which occurred in 90 per cent of subjects with clinical TD. This was chosen by calculating the neuroleptic exposure for all TD patients and the 90th percentile was found to be just below five years total exposure. Thus all subjects exposed to neuroleptics for at least five years or longer without developing TD were candidates for the control group providing they had been given the CLAT test prior to or at the time of entry into the study. There were 44 control subjects located who satisfied these criteria.

Results

There were no significant differences between the TD and control group on the variables of age, sex distribution, potency (high or low) of predominent neuroleptic used, or maximum sustained neuroleptic dose in CPZ equivalents over one month. The mean or proportionate values characterizing TD and control groups are summarized in Table 1. Because of the method of selecting controls, the control group was forced to have substantially longer cumulative neuroleptic exposures than the TD group. Indeed, only 10 per cent of the TD patients had exposures equivalent to the least exposed control subject.

The results of this investigation are shown in Table II

TABLE I

General aspects of subject groups

	Tardive dyskinesia	Control	
Mean age	32.4	28.9	N.S.
% female	47.1	45.5	N.S.
Potency of min neuroleptic (% high potency)	61.5	75.0	N.S.
Maximum one month sustained neuroleptic dose in mgms of chlorpromazine equivalent	1339	1615	N.S.

TABLE II

Conceptual level analogy test

	Baseline TD	Prospective TD	Control
Numbers of subjects	22	29	44
Number scoring:			
0–3	8	9	5
4–8	5	7	7
9 or over	9	13	32

N.B. On Cochran χ^2 for linear regression baseline TD versus controls was significant at $P < 0.01$, baseline TD versus prospective TD was non-significant and prospection TD versus controls, was significant at $P < 0.03$.

where the 3 × 3 contingency displays the Conceptual Level Analogy Test performance across TD and control groups. Because of important conceptual considerations to be mentioned, all cases of persistent TD were dichotomized into baseline and prospective TD categories as defined earlier. The Cochran χ^2 test for linear regression (Cochran, 1954) indicate that statistically significant positive associations exist between impaired CLAT performance and both baseline and prospective TD compared with controls. With baseline TD, its development preceeded CLAT testing and one might argue that the cognitive dysfunction found was but a correlated manifestation of the TD syndrome itself. That alone would be interesting but it would not allow a view of impaired CLAT score as predictive. With prospective TD cases, however, this is not true, because the CLAT results were secured well prior to the earliest evidence of TD. As such, impaired CLAT performance may suggest an "a priori" elevated degree of vulnerability to subsequent clinical TD although the magnitude of the statistical association we report does not permit prediction on an individual case basis. Also apparent in Table II is the fact that both baseline TD and prospective TD groups display essentially similar

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CLAT score distibutions and there is no significant difference between them regarding impaired performance on this instrument.

Earlier in this report we stated that subjects considered to display "transient" or "withdrawal" dyskinesia were omitted from the study. As a point of interest we decided to contrast the 17 omitted cases with "non-persistent" dyskinesia with the control group from Table II in terms of CLAT impairment. When this was done, no significant difference was found (χ^2 = 1.3731, d.f. = 1, P = N.S.). Apparently impaired CLAT performance may be strongly associated with persistent TD but not with non-persistent varieties of the TD syndrome.

Discussion

Not all patients exposed to neuroleptics develop TD. Furthermore patients have been exposed to neuroleptics for long periods without developing TD. Neuroleptics exposure is thus a necessary but not sufficient cause for this disorder. Rather neuroleptics and their dopamine blocking properties must interact with some pre-existing vulnerability for the syndrome to occur. As a sensitive and refined measure of abstracting ability, the CLAT is a useful tool in appraising brain function. Furthermore, there is empirical data which suggests that subcortical regions may also exert influences on what we term "cognitive" behavior (Oberg and Divac, 1979). It is thus conceivable that dysfunction in brain areas assumed to be associated with the pathophysiology of TD may be reflected by impairments on measures of higher function despite absence of clinically apparent impairment of cognitive status.

In our judgement our stringent criteria for defining a control subject increased experimental sensitivity sufficiently to allow detection of the significant differences we report. Control groups simply selected from patients without TD at the time of analyses, even when carefully matched with TD subjects on many variables, may be sufficiently "tainted" with patients who will later develop TD that genuine differences may not be visible. In our experience, whenever we have simply contrasted TD with non-TD patients we were unable to discern the relationship of CLAT performance to this disorder. Such failure was felt to be due to the limited exposure to medication (i.e. frequently less than one or two years) of large numbers of non-TD patients at the time of analysis.

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