The Dexamethasone Suppression Test and Depressive Signs in Dementia

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Summary

The non-suppression by dexamethasone of endogenous cortisol production has been held to be a specific and sensitive indicator of biological depression. Non-suppression has, however, been reported in a proportion of patients with severe dementia. In the present study failure of suppression was found in 10 out of 20 demented patients. The non-suppressors scored significantly higher on a scale of signs of depression. Following antidepressant treatment, 3 out of 8 non-suppressors reverted to normal suppression, but this was not associated with clinical improvements. The implications of these findings are discussed.

Key words: Antidepressant treatment – Dementia – Depressive signs – Dexamethasone Suppression Test

Introduction

A specific laboratory test of neuroendocrine function, the Dexamethasone Suppression Test (DST) has become widely used in the diagnosis of endogenous depression. An abnormal response, the early escape of endogenous cortisol production from suppression by orally administered dexamethasone (non-suppression), occurs in up to 67% of patients with endogenous depression and in as few as 4% of normal subjects or subjects with schizophrenia, neurosis or personality disorders (Carroll 1982).

The high specificity of the test lends it great promise in the differentiation between clinically similar presentations of different diagnoses. It has been shown to be abnormal in mixed affective states (Carroll 1979), in different proportions of the subtypes of endogenous depression (Schlesser et al. 1980) and in a high proportion of patients with schizo-affective psychosis (Schlesser M.A. (pers. comm.); Greden et al. 1981). The DST has been claimed to be of use in the differential diagnosis of geriatric patients whose clinical presentation is compatible both with dementia and depressive pseudo-dementia (McAllister et al. 1982; Jenike 1983). However, in 5 recent reports (Raskind et al. 1982; Spar and Gerner 1982; Baldin et al. 1983; Coppen et al. 1983; Carnes et al. 1983) approximately 50% of demented patients had an abnormal DST response (non-suppression).
Reus (1982) has raised doubts of a different nature as to the interpretation of abnormal DSTs. In a consecutive unselected series of acute adult admissions he found a considerable proportion of abnormal DSTs which were associated with “biological shift” (sleep and appetite disturbance, diurnal variation of mood etc.) with or without a diagnosis of depression.

The present study was designed to test a set of hypotheses that would reconcile the findings in dementia cited above.

1. The DST response is abnormal in a proportion of patients with a clinical diagnosis of dementia.

2. Demented patients with an abnormal DST response display greater evidence of depression than those with a normal DST.

3. Antidepressant treatment will lead to reversion to normal DST response in some demented patients and such reversion will be associated with improvement in behaviour and cognitive performance and in lessening of depressive signs.

Method

Selection of sample

The case notes of Fulbourn Hospital psychogeriatric in-patients were examined and a total of 20 patients found fulfilling the following criteria.

(a) Age over 70 years.

(b) Clinical diagnosis of dementia (Alzheimer type).

(c) No clinical evidence (on assessment by the responsible consultant) of current depressive illness.

(d) No evidence of endocrine disease or focal central nervous system abnormality.

(e) Not treated with barbiturates, anti-convulsants or steroids.

All the patients included had been ill for at least a year (range 1–11 yr; median 4.5 yr) and were severely demented. For the clinical ratings a control group of 10 depressed patients matched for age and with similar exclusion criteria was selected by the same means. It was not possible to perform DSTs on this group.

Dexamethasone Suppression Test

One milligram of dexamethasone was adminis-
**Cognitive rating**

The information/orientation scale of the Clifton Assessment Procedures for the Elderly (Pattie and Gilleard 1979) was administered to each subject jointly by the authors.

**Depression rating**

Since none of the currently available ratings of behaviour, cognitive function or depression appeared adequate for the assessment of depressive signs in a severely demented population, a 9-point depressive signs scale (DSS) was devised and rated jointly by the authors. In this way, inter-rater reliability could be calculated for individual items and the whole scale. The depressive control group was used to validate the scale.

**Treatment**

Patients showing DST non-suppression were treated with Dothiepin in a single night-time dose starting at 25 mg and increasing in twice weekly increments up to 100 mg or the maximum tolerated dose if lower. Treatment at the highest possible dose was continued for 4 weeks prior to re-assessment.

**Results**

**Dexamethasone Suppression Test**

Ten of 20 subjects with dementia fulfilled Carroll’s (1982) criteria for non-suppression (at least one post-dexamethasone cortisol level > 138 nmol/l). There were no significant differences (see Table 1) between the suppressor and non-suppressor groups in age or length of illness and none in scores on the cognitive and behaviour tests (Mann–Whitney U-test). There were also no significant correlations (Spearman’s rank order correlation coefficient) between mean post-dexamethasone cortisol levels and any of the above measures.

**Depressive Sign Scale (DSS)**

Inter-rater reliability for total DSS score as measured by Spearman’s rank order correlation coefficient was 0.98 for the demented patients (0.94 for the first 10 and 0.99 for the second 10) and 0.98 for the depressive controls ($P < 0.0001$ in each case). Linear weighted Cohen’s Kappa (Hall 1974) for the individual items of the scale (see Appendix) ranged between 1 and 0.71. DSS scores were distributed bimodally, with peaks at 1 and 4, in the demented patients, and unimodally with peak at 5 for the depressed controls (see Fig. 1). A significant difference (Mann–Whitney U-test, $P < 0.05$) was found in DSS scores between the depressed and demented groups.

**Cognitive and behaviour scores**

As can be seen from Table 1, none of the demented patients had a cognitive score greater than 3; indeed 13 out of 20 scored 0. The dementia sample also had high behaviour scores indicating severe disability. In contrast the depressed controls

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**TABLE 1**

**DST RESULTS AND CLINICAL DATA**

<table>
<thead>
<tr>
<th></th>
<th>Dementia (non-suppressors)</th>
<th>Dementia (suppressors)</th>
<th>Dementia (total)</th>
<th>Depressed controls</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Range (Median)</td>
<td>Range (Median)</td>
<td>Range (Median)</td>
<td>Range (Median)</td>
</tr>
<tr>
<td>Mean post-dexamethasone</td>
<td>134.5–345 (192.5)</td>
<td>32–103 (47.5)</td>
<td>32–345 (118.7)</td>
<td>1M, 9F</td>
</tr>
<tr>
<td>cortisol</td>
<td>2M, 8F</td>
<td>3M, 7F</td>
<td>5M, 15F</td>
<td></td>
</tr>
<tr>
<td>Sex</td>
<td>NS</td>
<td>NS</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>Age (yr)</td>
<td>71–95 (80.5)</td>
<td>67–93 (80)</td>
<td>67–95 (80.5)</td>
<td>68–87 (78.5)</td>
</tr>
<tr>
<td>Behaviour score</td>
<td>14–29 (23)</td>
<td>16–27 (20)</td>
<td>14–29 (22)</td>
<td>2–17 (9)</td>
</tr>
<tr>
<td>Cognitive score</td>
<td>0–2 (0)</td>
<td>0–3 (0.5)</td>
<td>0–3 (0)</td>
<td>8–12 (9.5)</td>
</tr>
<tr>
<td>DSS score</td>
<td>1–7 (4)</td>
<td>0–9 (1.5)</td>
<td>0–9 (4)</td>
<td>2.5–7 (5)</td>
</tr>
</tbody>
</table>

* Fisher’s exact test (score < 2 vs test), $P = 0.029$.
+ Mann–Whitney U-test, $P < 0.05$.
++ Mann–Whitney U-test, $P < 0.01$. 

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showed little or no cognitive defect although they had a wide range of behavioural disability.

Relationship between DSS score and Dexamethasone Suppression Test

DST non-suppressors tended (Fig. 2) to have higher DSS scores than suppressors. Rank order correlations between mean post-dexamethasone cortisol and DSS score ($r = 0.31$) and Mann-Whitney U-test comparison between suppressors and non-suppressors both just failed to reach statistical significance. However, re-analysis of the results in two groups using a cut-off score of 2 (the first peak on the distribution curve of DSS scores in the demented sample) yielded a significant difference (Fisher's exact test $P = 0.029$).

Response to treatment (see Table 2)

Two of the 10 DST non-suppressors could not be included in the open trial of Dothiepin (one patient was discharged home and one suffered from congestive cardiac failure). Postural hypotension and resultant falls limited the maximum

<table>
<thead>
<tr>
<th>TABLE 2</th>
<th>RESPONSE TO ANTIDEPRESSANT TREATMENT</th>
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<tbody>
<tr>
<td>DST (mean post dex. cortisol)</td>
<td>Cognitive score</td>
</tr>
<tr>
<td>Before</td>
<td>After</td>
</tr>
<tr>
<td>177.5</td>
<td>240.5</td>
</tr>
<tr>
<td>345</td>
<td>633</td>
</tr>
<tr>
<td>205</td>
<td>341</td>
</tr>
<tr>
<td>136.5</td>
<td>173</td>
</tr>
<tr>
<td>134.5</td>
<td>79</td>
</tr>
</tbody>
</table>

All before/after differences N.S. (sign test; signed rank test).
All reverters/non-reverters outcome comparisons N.S. (Mann-Whitney U-test).
maximum tolerated dose, 3 had reverted to normal suppression. Overall, however, antidepressant treatment failed to produce clinical improvement in terms of cognitive, behaviour or DSS scores. Reversion to normal suppression was also not associated with clinical improvement.

Discussion

The finding of a high rate (50%) of early escape of cortisol production from suppression by dexamethasone in an elderly demented population calls into question Carroll's (1982) claim concerning the high specificity for depression of DST non-suppression. The usefulness of the DST as a screening procedure in the elderly may well be less than that claimed by Georgotas (1983).

The presence of depressive illness is, however, difficult to detect in a severely demented population although depressive features are often noted in the early stages of the dementing process. Carnes et al. (1983) related DST non-suppression in demented outpatients with concurrent depression but their subjects had sufficiently preserved cognitive functioning to enable depressive symptoms to be elicited. Raskind et al. (1982) though noting DST non-suppression in 7 out of 15 demented patients failed to find any relationship with depressed appearance, and similar findings have recently been reported by Balldin et al. (1983). Our depressive signs scale may enable depression to be assessed without recourse to detection of symptoms by direct questioning of patients. It is possible that vulnerability to depression is increased in the presence of dementia as it is in other types of diffuse brain injury.

Our findings offer limited support for this hypothesis in that dexamethasone suppression test abnormality was associated with a high DSS score. The demonstration of a bimodal distribution of DSS scores in the dementia sample is itself suggestive of a subpopulation of demented patients with co-existent depression. Our results failed to demonstrate any significant relationship, or even trend, between DST results and degree of dementia or age. The latter finding is in contrast with that of Spar and Gerner (1982) but accords with the findings of Tourigny-Rivard et al. (1981) in a group of normal elderly. It, therefore, seems unlikely that the DST abnormalities we have demonstrated are directly related either to the dementing process or to normal aging.

Our study has lent some support to the first two hypotheses listed earlier in the paper in that a high rate of DST abnormality was demonstrated, associated with an increase in signs of depression (assessed blind to DST results). Support for the third hypothesis was less clear; three patients reverted to normal suppression, though changes in cortisol levels were small, but there was no evidence of clinical improvement.

Alternative explanations for our findings must be considered. It is unlikely that the dementia sample was contaminated by mis-diagnosed depressives, in view of the profound degree of the dementia and the poor response to antidepressant treatment. Poor tolerance of the antidepressant used may have limited the therapeutic potential of antidepressant treatment, though this was surprising in view of previous reports (Khan 1975, 1981) that Dothiepin is well tolerated in elderly depressives.

Despite the limitations of our study, the finding of an association between DST abnormality in dementia and evidence of excess signs of depression, as well as the reversion to normal of DST result in some cases following antidepressant treatment at least suggests that DST abnormality in dementia reflects a coexistent disorder of affect. Our depressive signs scale may provide a useful clinical screening test in patients diagnosed as having dementia. We are hoping to carry out a further study in a larger sample of patients with a less severe degree of dementia who may be both more responsive to and better able to tolerate tricyclic antidepressant treatment.

Appendix

Depressive Signs Scale

Each item to be rated following clinical interview with subject and interview with nursing staff (or relative in the case of out-patients) directly involved in caring for the subject.
Definition of items and scoring

N.B. For all items the relevant period is the past week.

1. Sad appearance
Gloom, despair, tearfulness, despondency as suggested by facial expression and posture.
- Marked = 2
- Intermediate = 1
- Absent = 0

1.1 Reactivity of sad appearance. Alleviation of sad appearance by external circumstances (do not score if no evidence of sad appearance).
- Absent = 1
- Present = 0

2. Agitation by day
Agitated, pacing, wringing hands, picking at clothes, hair; calling out without reason (except in response to being moved etc.).
- Persistent and extreme = 2
- Mild or intermittent = 1
- Absent = 0

3. Slowness of movement
Motor inhibition, evidenced by slowing of physical reactions: excessive slowness in walking, eating, gesturing etc. other than slowness due to physical disability. Physical examination may be necessary. Change in the absence of physical deterioration may be crucial.
- Marked = 2
- Intermediate = 1
- Absent = 0

4. Slowness of speech
Excessive latency of speech: slowness of speech, or low or monotonous speech, other than due to physical disability. Change in the absence of physical deterioration may be crucial.
- Marked = 2
- Intermediate = 1
- Absent = 0

5. Early waking
Difficulty in staying asleep beyond 5.00 a.m. or final waking before 5.00 a.m. irrespective of night sedation. This item requires checking by night nursing staff to verify waking/sleep.
- Consistent = 2
- Intermittent = 1
- Absent = 0

6. Loss of appetite
Diminished interest in food or diminished food intake. Weight loss is relevant if it can be elicited but allowance must be made for physical causes.
- Marked = 2
- Intermediate = 1
- Absent = 0

7. Diurnal variation in mood (mornings worst)
Facial appearance and demeanour suggests consistently maximal depression in the mornings with clear improvement in the course of the day. Rate as absent if purely a reaction to circumstances.
- Marked = 2
- Intermediate = 1
- Absent = 0

8. Interest in surroundings
Including watching TV, food, interesting conversation. It is the maximum degree of interest and attention in response to any stimulus that is being measured.
- Never = 2
- Occasional = 1
- Equally = 0

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References


