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Age and gender effects on the diagnostic power of the DST

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Summary

Among 365 major and 158 minor depressive inpatients, the dexamethasone suppression test (DST) yielded an overall diagnostic sensitivity of 50%, a specificity of 85%, and a confidence level of 88%. Age was significantly correlated with the post-dexamethasone cortisol levels in the whole sample (r = 0.11; P < 0.01); however, this low relationship disappeared when all subgroups defined by gender or diagnostic were considered. Gender did not appear to influence DST results; however, among the patients between 30 and 39 years, the diagnostic performance of the DST was significantly lower among female as compared to male patients, suggesting possible interferences with endocrine variables.

Key words: Dexamethasone suppression test; Aging; Gender; Major depression; Minor depression

Introduction

The overnight dexamethasone suppression test (DST) currently represents the most widely used biological marker for major, primary, or endogenous depression (review in Carroll 1982; Arana et al. 1985; Braddock 1986). About 50% of major, primary, or endogenous depressives exhibit an abnormal cortisol 'escape' from dexamethasone suppression; however, the specificity of this phe-

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nomenon is still debated (review in Hirschfeld et al. 1983). Among other confounding factors, the role of age and gender in the cortisol response to dexamethasone in depressive patients is still a subject of controversies.

Concerning age, the initial studies with the DST did not demonstrate a significant influence of this parameter on DST results (Carroll et al. 1982; Mendlewicz et al. 1982) but more recent studies suggested a relationship between age and cortisol level following dexamethasone (Asnis et al. 1981; Brown and Qualls 1981; Davis et al. 1984; Lewis et al. 1984; Nelson et al. 1984a, b; Stokes et al. 1984; Fogel and Satel 1985; Fogel et al. 1985) and that DST nonsuppression might be

associated with significant older age (Brown and Qualls 1981; Zimmerman et al., 1986; Ansseau et al. 1986a; Baumgartner et al. 1986).

Concerning gender, earlier studies mentioned the importance of this variable in the steroid secretion of both normal subjects (Sachar et al. 1965; Curtis et al. 1966) and depressive patients (Fullerton et al. 1968) and a significant interaction between age and baseline cortisol values as well as nonsuppression rates was found in depressed males but not in depressed females (Nelson et al. 1984a, b). A recent study also suggested a better diagnostic value of the DST in younger men and less so in younger women or older men and women (Halbreich et al. 1986). Moreover, a multicenter study found that unipolar depressed women had higher basal plasma and urinary cortisol levels than unipolar men; in addition, a modest gender difference was seen in all depressed (unipolar and bipolar) patients on post-DST morning plasma cortisol levels (Stokes et al. 1984). However, most studies did not find gender-related differences in DST results (Brown and Qualls 1981; Carroll et al. 1981; Gwirstman et al. 1982; Mendlewicz et al. 1982; Feinberg and Carroll 1984; Nelson et al. 1984b).

In this context, the purpose of our study was to assess specifically the influence of age and gender in the diagnostic power of the DST for the diagnostic confirmation of major depression.

Patients and methods

Subjects

A total of 523 depressive patients, consecutively admitted to 6 University-affiliated departments of psychiatry were included in the study. According to the Research Diagnostic Criteria (Spitzer et al. 1978), 365 patients exhibited a major depressive episode and 158 patients suffered from minor depression. All diagnostic procedures were done by trained psychiatrists not aware of laboratory results. The whole sample included 160 male and 363 female patients: 103 males and 262 females among major depressives and 57 males and 101 females among minor depressives. Mean age was significantly older in the major depressive as compared to the minor depressive groups: 48.5 years \pm 14.4 vs. 42.5 years \pm 13.0, t = 4.5, df = 521,

P < 0.001. All patients were newly admitted and the DST was performed after a drug-free period of at least one week. The subjects presenting evidence of medical illness on clinical examination, electrocardiogram, electroencephalogram, chest X-ray, and routine laboratory tests were excluded from the study. Moreover, all the exclusion criteria defined by Carroll et al. (1981) were carefully applied. All patients were fully informed regarding the study and gave their consent.

DST procedure

The DST was performed according to the simplified procedure described by Carroll (1982). Oral dexamethasone (1 mg) was administered by a nurse at 11 p.m. and a post-dexamethasone sample was collected at 4 p.m. the following day. Nonsuppression was defined as a cortisol level $> 5 \mu g/dl$.

Cortisol assay

Plasma cortisol was measured by direct radioimmunoassay (RIA) from samples of 25 μ l, 40-fold diluted, and heated at 60 °C for 30 min. RIA used [125 I]cortisol (Farmos Diagnostica, Finland) and anticortisol antiserum (made against the 3-CMO-BSA conjugate), as described previously (Sulon et al. 1978). All samples were processed in duplicate, with a maximum intra- and inter-assay coefficient of variation of 4.3% and 8.3%, respectively, and a detection limit of 2.0 μ g/dl.

Data analysis

Sensitivity, specificity, and diagnostic confidence of the DST for major depression were calculated according to the definition of Vecchio (1966), with an illness prevalence of 50% for diagnostic confidence.

The differences in cortisol levels between the two groups were analysed using group *t*-tests (two-tailed) while the distributions of DST suppressors and nonsuppressors were compared using the Chi-square statistics. This last method was also applied among younger (< 50 years) and older (> 50 years) patients as well as in younger and older male and female patients. The same analysis was also performed using 55 years as cut-off age but since the results were quite similar, they will not be reported herein. The relationship

between cortisol levels following DST and age was assessed by the Pearson's product moment correlation coefficient. Finally, a discriminant analysis was performed using the diagnostic subgroup as independent variable and the DST results (suppressor vs. nonsuppressor), gender, and age (each decade) as dependent variable. As cortisol concentrations tended to be log-normally distributed, the data were analysed by using a natural log transformation.

Results

The mean cortisol level following DST was significantly higher among major as compared to minor depressive patients: 7.05 μ g/dl \pm 7.2 vs. 3.67 μ g/dl \pm 5.1, t = 5.3, df = 521, P < 0.001. A total of 183 major depressive and 24 minor depressive patients were nonsuppressors ($\chi^2 = 56.3$, P < 0.00001). These results yielded an overall diagnostic sensitivity of 50%, specificity of 85%, and confidence of 88%.

The distribution of suppressor and nonsuppressor major and minor depressives among younger (< 50 years) and older (> 50 years) subjects as well as among male and female patients is presented in Table 1. For younger patients, the diagnostic sensitivity of the DST was quite similar in males and females (47 and 48%); however, in older patients, it was higher in females than males (58 vs. 38%). The diagnostic specificity was clearly higher in male than in female patients, particularly in younger (95 vs. 78%) but also in older patients (92 vs. 82%).

The comparison of the distribution in various age groups of DST suppressor and nonsuppressor male and female patients with major and minor depression is presented in Table 2. No statistical difference was present among major depressive patients; however, the proportion of minor depressive patients with DST nonsuppression was clearly higher among female patients (P = 0.006) and the stratification by age groups showed that this difference was most apparent among the patients between 30 and 39 years (P = 0.04). These results are confirmed by the comparison of the diagnostic performance of the DST in male and female patients of various age groups (Fig. 1). Among patients between 30 and 39 years, the sensitivity and specificity of the DST for the diagnostic confirmation of major depression were clearly higher in male as compared to female depressives: 58% vs. 30% for sensitivity and 100% vs. 70% for specificity.

Age was significantly correlated with the cortisol level following DST for the whole sample (r = 0.11, n = 523, P = 0.003). However, this relationship lost statistical significance when the sample was divided according to gender (r = 0.12, n = 160, P = NS) in males and r = 0.08, n = 363, P = NS in females) as well as according to diagnostic groups (r = 0.08, n = 365, P = NS) among major depressives and r = 0.05, n = 158, P = NS among minor depressives).

Finally, the discriminant analysis using the diagnostic subgroup as independent variable showed significant roles for DST results (F = 57.3) and

TABLE 1

COMPARISON OF THE DISTRIBUTION OF DST SUPPRESSORS (S) AND NONSUPPRESSORS (NS) IN MAJOR AND MINOR DEPRESSIVES AND DIAGNOSTIC PERFORMANCE OF THE DST FOR MAJOR DEPRESSION

	Major	depressives	Minor	depressives	χ^2	P	Sensitivity	Specificity	Diagnostic confidence (%)	
	S	NS	S	NS			(%)	(%)		
Younger (< 50)			9 8					2	L	
males	31	27	42	2	а	< 0.00001	47	95	93	
females	65	59	53	15	12.1	< 0.0005	48	78	80	
total	96	86	95	17	31.3	< 0.00001	47	85	83	
Older (> 50)		r.			42 19				20 ⁶	
males	28	17	12	1	a	NS	38	92	94	
females	58	80	27	6	16.8	< 0.00001	58	82	93	
total	86	97	39	7	21.1	< 0.00001	53	85	93	

a Exact Fisher's test.

TABLE 2
COMPARISON OF THE DISTRIBUTION OF DST SUPPRESSOR (S) AND NONSUPPRESSOR (NS) MALE AND FEMALE MAJOR AND MINOR DEPRESSIVES OF VARIOUS AGE GROUPS

	4	Males			Females				χ^2			P		
		S		****	NS		S	NS		90		*	E	W
Major depressives	87		2.	24									20	18
age < 30	, P	. 7			3		16	13	3		а	N 18	NS	
30-39		11		*	15		23	25	5 .		0.1		NS	
40-49		13			9	(9) (8)	26	2	l		0.0		NS	
50-59		16			12		27	42	2		1.9		NS	
> 60		12	300		5		30	38	3		0.3		NS	
total	a A	59			44	2.5	123	139)		2.8		0.10	
Minor depressives							* **	A.C.					1	
	ok o	9			1		15	1	2		a		NS	
30-39	N.	17	150		0		19		3		a		0.04	
40-49	18/4	16			1		19		5		a		NS	
50-59		9	19	19	0		17		2		a	380 (6)	NS	
> 60	5 54	3			1		10		4	N	a		NS	
total		54			3		80	2:	1		а	*	0.006	e e

a Exact Fisher's test.

age (F = 15.8) but no significant association with gender (F = 0.2). The diagnostic was correctly

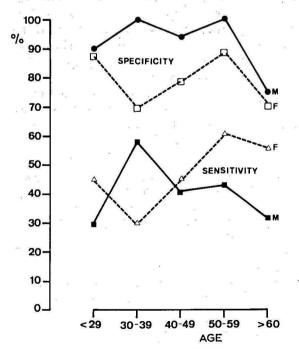


Fig. 1. Diagnostic performance of the DST in relation to age among male (M) and female (F) major vs. minor depressive patients.

predicted from DST results and age in 62% of major and 77% of minor depressive patients.

Discussion

This large-scale evaluation of the diagnostic performance of the DST for major vs. minor depression yields an overall sensitivity (50%) and specificity (85%) rather close to the mean diagnostic performance recently obtained from a literature review (Arana et al. 1985): sensitivity of 44% and specificity of 77%. The slightly better results may be due to the sole inclusion of inpatients in our study. Indeed, there is large evidence that studies with outpatients yield a lower overall performance than studies with inpatients (Carroll 1982). This may be due to the inclusion of outpatients with less symptom severity and less control of possible confounding factors such as drug compliance and drug association.

Our study does not demonstrate a strong effect for age in DST results. Indeed, the relationship between age and cortisol levels following DST is low for the whole sample (r=0.11) and disappears when subgroups defined by diagnosis or gender were considered. The statistical significance observed for the whole sample may depend on the one hand on the large number of subjects

tested (523) and on the other hand on the inclusion of 2 diagnostic groups: major depressive patients characterized by older age and higher cortisol levels and minor depressive patients characterized by younger age and lower cortisol levels. The effect of age on DST results among major depressive patients is controversial. The initial studies of Carroll et al. (1981) and of Mendlewicz et al. (1982) concluded that age had no effect on cortisol levels and DST results in depressive patients. However, other authors found a significant correlation between post-dexamethasone cortisol values and age (Asnis et al. 1981; Davis et al. 1984; Lewis et al. 1984; Nelson et al. 1984a, b; Stokes et al. 1984; Fogel and Satel 1985; Fogel et al. 1985) and older age among nonsuppressor depressives (Brown and Qualls 1981; Ansseau et al. 1986a; Baumgartner et al. 1986; Zimmerman et al. 1986). In normal subjects, most studies failed to demonstrate a significant role for age in the 1 mg DST (Tourigny-Rivard et al. 1981; Lewis et al. 1984; Stokes et al. 1984; Fogel et al. 1985; Ansseau et al. 1986b) but divergent results were obtained by Oxenkrug et al. (1983) who utilized 0.5 mg dexamethasone and a post-DST sample 9 h later, and by Rosenbaum et al. (1984) with the standard DST procedure but only if the cortisol levels were measured by radioimmunoassay and not by the competitive protein binding method. In this latter study, age did not appear to have a general effect on increasing cortisol production since weaker and often nonsignificant correlations were obtained between pre-dexamethasone values and age. The authors hypothesized that these differences could be related to the poor absorption of dexamethasone in older subjects. However, several studies have reported a relationship between age and basal cortisol secretion in depressive patients (Asnis et al. 1981; Davis et al. 1984; Halbreich et al. 1984; Stokes et al. 1984) while Branconnier et al. (1984) found that basal cortisol levels were significant predictors of post-dexamethasone cortisol levels in normal subjects. However, these latter authors used 0.5 mg dexamethasone with a morning post-DST sample and Ansseau et al. (1986b) were unable to replicate these findings using a more standard DST procedure (1 mg dexamethasone and 4 p.m. post-DST sample). Moreover, Tourigny-Rivard et al. (1981) did not

find any difference in cortisol secretion both before and after DST in 10 elderly as compared to 10 young healthy subjects. Unfortunately, a predexamethasone blood sample was not collected in our study, preventing us from testing possible relationships between basal cortisol and age as well as post-DST cortisol levels.

Our study does not demonstrate overall differences related to gender in DST results. These findings are in agreement with previous studies which did not find gender-related differences in DST performance (Brown and Qualls 1981; Carroll et al. 1981; Gwirtsman et al. 1982; Mendlewicz et al. 1982; Feinberg and Carroll 1984; Nelson et al. 1984b). However, a small study of Bryer et al. (1983) showed that nonsuppressor depressives were more likely to be female while Stokes et al. (1984) found that the morning post-dexamethasone cortisol levels were significantly higher in female as compared to male depressives. Nelson et al. (1984a) suggested that gender might be a critical issue in the controversies concerning an age-related effect in DST results. They found a significant interaction between age and baseline cortisol values and nonsuppression rates in depressed males but not in nondepressed males nor in depressed and nondepressed females. These results confirm the hypothesis of Brown and Qualls (1981) that gender differences between study populations are a factor in the age-cortisol correlation. Only in subject populations with a preponderance of women has the association between age and hypothalamo-pituitary-adrenal (HPA) axis activity been noted. A possible explanation for these findings is suggested by Robinson et al. (1977) and Carlsson et al. (1980) who found that normal older subjects exhibited significantly decreased brain norepinephrine levels and an increased monoamine oxidase (MAO) activity. Because decreased brain norepinephrine may cause depression as well as HPA axis desinhibition (Ganong 1972), one would predict the observed increased incidence of depression with age and frequent HPA axis overactivity in the older depressives. Because MAO activity is greater in the older woman (Robinson et al. 1977; Carlsson et al. 1980), this group would be at highest risk for depression and cortisol hypersecretion.

Our study shows gender-related differences in

DST results among the age group from 30 to 39 years. Within the age range, both sensitivity and specificity of the DST are significantly lower in female than in male patients, supporting recent findings of Halbreich et al. (1986). This poor diagnostic performance of the DST among this female age group may be due to interference of the cortisol assay with sexual steroids secreted at different levels during the menstrual cycle. Indeed, in this study we measured the total level of cortisol while the biological activity of steroids parallels the 'free' hormone concentration. Transcortin binds cortisol with a high affinity, and in basal conditions, nearly all the binding sites for cortisol are occupied. However, for a given transcortin concentration, the number of binding sites available for cortisol can be modified by the level of other steroids competing for the same sites (e.g., progesterone, 17-hydroxyprogesterone). A clearcut decrease in the binding capacity of transcortin has also been described in depressive patients (Ktiouet et al. 1984). Moreover, the intake of oestrogen-containing oral contraceptives can alter the level of total cortisol due to increased synthesis of transcortin (Demey-Ponsart et al. 1977). Even if the intake of oral contraceptives was an exclusion criterion in our study, it remains possible that some patients were taking them without the clinician's knowledge. Possible ways to circumvent these confounding factors include the measurement of plasma free cortisol itself (Charles et al. 1986), urinary cortisol (Charles et al. 1981) or saliva cortisol (Ansseau et al. 1984), directly related to plasma free cortisol.

In conclusion, this study suggests little age effect on the diagnostic power of the DST but interference from endocrine factors among female patients cannot be excluded.

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