Eur Psychiatry (1994) 9, 195–200

Original article

Transcultural approach of depression. Comparative study of the diagnostic performance of the dexamethasone suppression test in São Paulo (Brazil) and Liège (Belgium)

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(Received 3 February 1993; accepted 8 December 1993)

Summary – We compared the rate of DST non-suppression in two samples of 26 Brazilian and 26 Belgian female depressive patients, matched for age, diagnostic subtype and severity of depression. This rate was significantly lower in São Paulo than in Liège ($P = 0.04$). The differences observed in DST can be explained by the complexity of familial, personal and clinical factors. A role of a latitude effect through melatonin secretion on adrenocortical function of depressed patients is also suggested.

dexamethasone suppression test / major depression / seasonality / transcultural approach

Introduction

The dexamethasone suppression test (DST) has been proposed as a "biological marker" of major or endogenous depression with a diagnostic sensitivity ranging from 40 to 70% (Carroll *et al*, 1981). The specificity of the DST remains however very controversial (Braddock, 1986; American Psychiatric Association, 1987). Numerous factors can induce "false-positive DSTs". Thus, stressful life-events, stress of hospital admission as well as numerous drugs are able to alter the response to DST. Controversial data also exist concerning possible clinical correlates of DST non suppression. Some results implicated a role for age, severity and subtype of depression, number of previous episodes and psychiatric family history (review in Cohen *et al*, 1988). However, the role of both cultural and geographic factors is not yet well known. Several collaborative studies showed different rates of abnormal DST results in different centers (WHO 1987; Stokes *et al*, 1984). Upon inspecting the data, Rihmer (1987) hypothesized that cities closer to the equator showed less frequent abnormality in their corticol secretion patterns. He also noticed that studies in the southern hemisphere were very sparse.

In the framework of a co-operative project, created between Belgium (French Community) and Brazil, we had the opportunity to compare two samples of depressive patients, from Liège (Belgium) and São Paulo (Brazil) regarding their biological, clinical and psychological features. The purpose of this study was to report our first results concerning their DST data and their clinical correlates.

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Method

Subjects

The sample comprised 52 female patients, 26 Brazilian and 26 Belgian. The choice of female patients aims to check a possible variability induced by the sex and was justified by the fact that epidemiologic studies show a predominant incidence of depression in women (Cohen, 1967).

Women patients, who fulfilled the DSM III criteria for major depressive episode were included in the sample. The subjects were matched for age (39.9 ± 5.7 in Brazil and 41.6 ± 9.2 in Belgium, $F = 0.63$, P = ns), for diagnostic subtype (melancholia) and for severity of depression (they all had a score of at least 24 on the Hamilton depression scale (Hamilton, 1960; Dractu *et al*, 1985).

We excluded patients exhibiting endocrine or metabolic diseases, brain organic disturbances or alcoholic and toxicomaniac habits.

Procedure

The group was submitted to a very complete psychiatric and psychological anamnesis, including familial and personal history which helped to obtain, among others, information such as: – whether the patient was hospitalized or not; – type of depression – uni or bipolar; – whether she was having the first depressive episode or if she had previous episodes; – psychiatric cases in the family. In addition, demographic data (ethnic and sociocultural) were collected. The existence of stressful life-events related to the present depressive episode was considered according to Axis IV of DSM III (gravity of psychosocial stressors – of at least level 3 – moderate). The Montgomery and Asberg depression scale (MADRS) (Montgomery and Asberg, 1979) were also completed. The Collected data are summarized in table I.

DST – After a wash-out period of at least two weeks, the DST was performed according to the simplified procedure described by Carroll *et al* (1981): oral dexamethasone 1 mg was administered at 23 h and a post-dexamethasone sample was collected at 16 h on the following day. Cortisol was measured using a radioimmunoassay (RIA) method developed by Sulon *et al* (1978), with intra- and interassay coefficients of variation of 4.3 and 8.3% respectively. Non-suppression was defined as a plasma cortisol level higher than 5, μg/dl (Carroll *et al*, 1981). The assay method was conducted separately in the two laboratories.

Data analysis

The statistical analysis was performed with χ^2 and analysis of variance (Anova).

Results

DST

The rate of DST non-suppressors (NS) was significantly lower in São Paulo as compared to Liège: 5/26 *vs* 15/26, as shown in figure 1 (19.2% *vs* 57.7%, $\chi^2 = 8.1$, df = x, $P = 0.04$). (See summarized data in fig 1).

The level of Post-Dexamethasone cortisol of five Brazilian and the 15 Belgium NS patients did not show any difference (São Paulo NS = 10.5 ± 5 *vs* Liège NS = 11 ± 5). As several authors suggested that different clinical laboratories should differentiate NS from Suppressors (S) by locally defining an RIA-determined plasma level cut-off, we tested different cut-off values. The results are shown in figure 2. (See summarized data in fig 2).

The results remain significant even with the lowest cut-off level (34.7% in São Paulo *vs* 57.7% in Liège, $\chi^2 = 2.78$, $P = 0.09$).

Ethnic and socio-cultural characteristics

The São Paulo group was more heterogenous than the Liège group. It included 21 Caucasians, three Mulattos, one Black and one Japanese while the Liège group included 26 Caucasians. The monthly income of the São Paulo group ranged from 60 to 200 dollars while the income of the Liège group ranged from 500 to 4.500 dollars. The education level was also lower in São Paulo.

Hospitalization

Six patients in São Paulo and all the patients in Liège were hospitalized ($\chi^2 = 32.5$, df = x, $P = 0.0001$).

Unipolar vs *bipolar subtype*

The São Paulo group included 22 unipolar and four bipolar depressives as compared to 20 unipolar and six bipolar depressives in Liège ($\chi^2 = 2.50$, df = x, NS).

Stressful life-events

There was no significant difference between the Brazilian and Belgium samples: eight patients in the São Paulo group and ten in the Liège group exhibited stressful life-events that could have contributed to the development of the depressive episode (rating of at least 3-moderate on DSM III axis IV). ($\chi^2 = 0.33$, df = x, $P = 0.56$, NS).

Number of previous episodes

Six patients in São Paulo and six patients in Liège were in their first depressive episode;

Table I. Description of the collected data. 1) Nat – Nationality; 2) Etn – Ethnic – Cau: Caucasians, Bl: Black, Mul: Mulatto, Jap: Japanese; 3) Age; 4) Ham – Score of Hamilton's depressive scale; 5) Status – Patient's status: In or Out patient; 6) Dep: type of depression: Unipolar or Bipolar; 7) Ep Num – episode number – 1: first episode, 2 or 3: two or three episodes; + of 3: more than three episodes; 8) Fam His – psychiatric cases in the family – Dep: depressive cases; Alc: alcoholic cases; Schizo: history of schizophrenia; 9) Stress – existence (Yes) or not (No) of stressful live events; 10) MADRS – Montgomery and Asberg depression scale; 11) DST: value of DST; 12) S/NS – suppressor/nonsuppressor.

	Nat	*Etn*	*Age*	*HAM*	*Status*	*Dep*	*Episode number*	*Family history*	*Stress*	*MADRS*	*DST*	*S/NS*
1	Bra	Cau	44	44	Inpat	Uni	1	•	No	38	13,220	NS
2	Bra	Cau	34	48	Inpat	Uni	1	Alc	Yes	37	716	S
3	Bra	Cau	43	43	Outpat	Uni	2 or 3	Schizo	No	36	4369	S
4	Bra	Cau	39	39	Outpat	Uni	2 or 3	Alc	No	32	1991	S
5	Bra	Cau	51	29	Outpat	Uni	1	Alc	Yes	24	1660	S
6	Bra	Cau	33	32	Outpat	Uni	2 or 3	Dep	No	29	1739	S
7	Bra	Cau	35	43	Outpat	Uni	2 or 3	Dep	Yes	36	1631	S
8	Bra	Cau	50	33	Outpat	Uni	1	Alc	No	23	628	S
9	Bra	Cau	34	45	Inpat	Bi	2 or 3	Alc	No	43	2671	S
10	Bra	Cau	39	35	Outpat	Uni	1	•	No	31	1338	S
11	Bra	Cau	40	31	Outpat	Uni	2 or 3	Schizo	No	34	1843	S
12	Bra	Mul	40	31	Outpat	Bi	2 or 3	•	No	32	1950	S
13	Bra	Cau	50	34	Outpat	Uni	2 or 3	•	No	36	1376	S
14	Bra	Cau	43	30	Outpat	Uni	2 or 3	•	Yes	38	2203	S
15	Bra	Cau	40	43	Outpat	Uni	2 or 3	Schizo	Yes	34	492	S
16	Bra	Cau	39	30	Outpat	Uni	2 or 3	Alc	Yes	26	1252	S
17	Bra	Cau	34	45	Outpat	Uni	2 or 3	•	Yes	39	3550	S
18	Bra	Mul	40	40	Outpat	Uni	2 or 3	Alc	No	43	6560	NS
19	Bra	Jap	36	36	Inpat	Bi	+ of 3	Dep	No	38	3177	S
20	Bra	Cau	35	29	Outpat	Uni	2 or 3	Schizo	Yes	30	2133	S
21	Bra	Cau	30	41	Outpat	Uni	2 or 3	Dep	No	42	3273	S
22	Bra	Cau	33	34	Outpat	Uni	2 or 3	Schizo	No	27	1124	S
23	Bra	Cau	42	47	Inpat	Uni	2 or 3	Schizo	No	42	9932	NS
24	Bra	Mul	44	38	Outpat	Uni	1	•	No	30	5703	NS
25	Bra	Bla	48	55	Inpat	Bi	+ of 3	Schizo	No	46	17590	NS
26	Bra	Cau	42	34	Outpat	Uni	2 or 3	•	No	24	1857	S
27	Bel	Cau	52	24	Inpat	Bi	+ of 3	Dep	Yes	21	5900	NS
28	Bel	Cau	33	46	Inpat	Bi	1	Dep	No	40	14200	NS
29	Bel	Cau	53	38	Inpat	Bi	+ of 3	•	No	44	5600	NS
30	Bel	Cau	24	24	Inpat	Uni	1	Dep	Yes	27	9900	NS
31	Bel	Cau	52	32	Inpat	Uni	+ of 3	•	No	39	8800	NS
32	Bel	Cau	41	45	Inpat	Uni	2 or 3	•	Yes	48	6700	NS
33	Bel	Cau	48	37	Inpat	Uni	+ of 3	Dep	No	37	10400	NS
34	Bel	Cau	51	39	Inpat	Uni	2 or 3	Dep	No	35	2000	S
35	Bel	Cau	39	36	Inpat	Uni	+ of 3	•	Yes	41	2200	S
36	Bel	Cau	52	31	Inpat	Uni	2 or 3	Dep	No	42	10800	NS
37	Bel	Cau	51	37	Inpat	Bi	+ of 3	Alc	No	32	25900	NS
38	Bel	Cau	31	43	Inpat	Bi	2 or 3	•	Yes	50	12700	NS
39	Bel	Cau	46	34	Inpat	Bi	+ of 3	•	No	22	2700	S
40	Bel	Cau	41	42	Inpat	Uni	2 or 3	•	No	42	2000	S
41	Bel	Cau	49	44	Inpat	Uni	2 or 3	•	No	36	13900	NS
42	Bel	Cau	33	37	Inpat	Uni	1	•	No	32	2000	S
43	Bel	Cau	38	35	Inpat	Uni	+ of 3	Dep	No	43	8200	NS
44	Bel	Cau	38	29	Inpat	Uni	2 or 3	Dep	Yes	27	2600	S
45	Bel	Cau	49	48	Inpat	Uni	1	Dep	No	48	2300	S
46	Bel	Cau	27	43	Inpat	Uni	2 or 3	Dep	Yes	38	14100	NS
47	Bel	Cau	39	34	Inpat	Uni	+ of 3	•	Yes	21	2000	S
48	Bel	Cau	24	27	Inpat	Uni	1	Dep	No	31	10100	NS
49	Bel	Cau	51	47	Inpat	Uni	2 or 3	•	Yes	43	2000	S
50	Bel	Cau	34	36	Inpat	Uni	+ of 3	Dep	No	39	2000	S
51	Bel	Cau	48	28	Inpat	Uni	1	•	Yes	25	2000	S
52	Bel	Cau	38	35	Inpat	Uni	+ of 3	Dep	No	38	8800	NS

18 patients in São Paulo and nine in Liège were in their second or third depressive episode; two patients in São Paulo and 11 patients in Liège had more than three previous depressive episodes. In total, the Liège patients showed significantly more depressive occurrences than the Liège

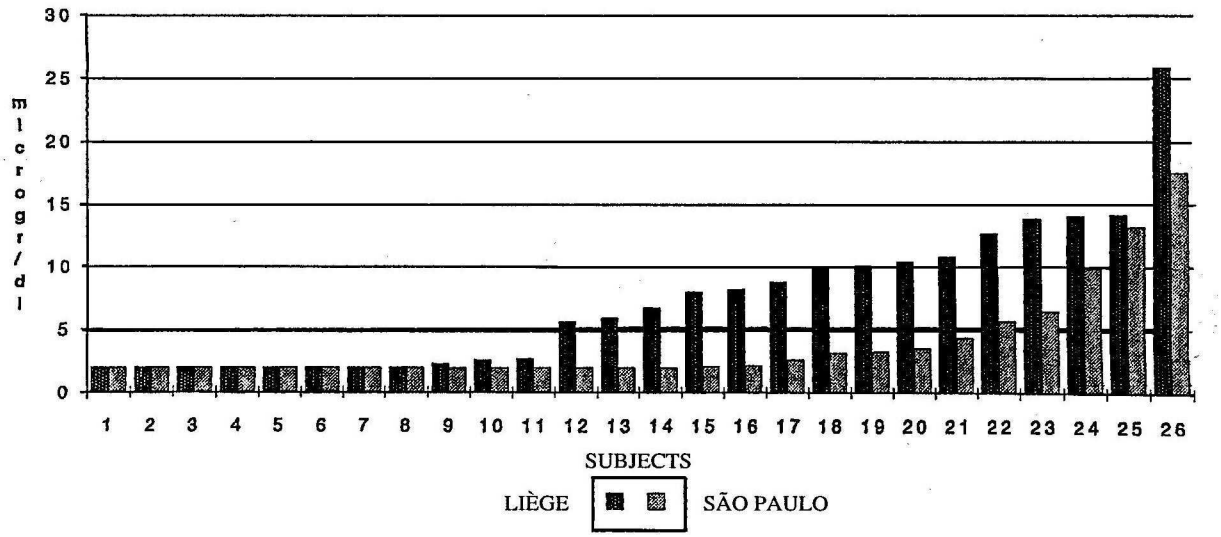

Fig 1. Description of individual plasma cortisol data measured 17 hours after the administration of dexamethasone in Liège and São Paulo depressive patients.

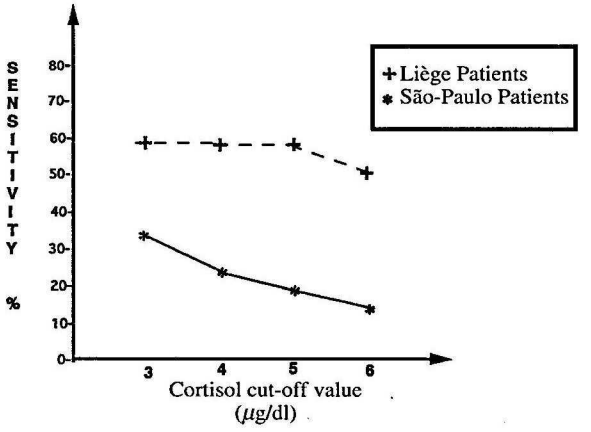

Fig 2. Comparative sensitivity of the DST among major depressive patients from São Paulo and Liège.

patients. (χ^2 = 18.03, *df* = x, *P* = 0.0001), *ie*, more than three episodes.

Family history

Four patients in São Paulo and 13 in Liège exhibited family history of depression; eight patients in São Paulo and one in Liège had a family history of alcoholism; seven patients in São Paulo and no patients in Liège exhibited a family history of schizophrenia. In total, a family history of psychiatric disorder was significantly more frequent in the São Paulo group than in the Liège group (χ^2 = 16.1, *df* = x, *P* = 0.0003). On the other hand, the family history of depression was predominant in the Liège sample.

Symptom severity

Mean MADRS scores did not significantly differ between the São Paulo and Liège groups. Their scores ranged from 23 to 46 in São Paulo (mean = 34.2 ± 6.4) and from 21 to 50 in Liège (mean = 36.2 ± 8.4; *t* = 0.89). However, when all patients were considered as a whole group, NS displayed a higher MADRS score than S (NS = 38 ± 7 vc S = 33 ± 7; *P* = 0.01).

Discussion

The results of this study show a significantly lower rate of NS depressive patients in a sample from São Paulo, as compared to a sample from Liège. This study used the classical cortisol cut-off level proposed by Carroll *et al* (1981) to define cortisol

non-suppression. However, a recent study performed in the same São Paulo laboratory in which the DST of the Brazilian sample was performed, selected a cortisol cut-off level of 3 μg/dl (Calil and Dractu, 1986). This study was carried out according to the recommandations of Meltzer *et al* (1983) and Carroll *et al* (1986) who strongly advised to select a locally established cut-off score. Using this cut-off score, the number of NS depressive patients in São Paulo would be increased to nine without modification in Liège, still showing a trend toward a significant difference in DST sensitivity between the two countries: 34.7% in São Paulo *vs* 57.7% in Liège, $\chi^2 = 2.78$, $P = 0.09$.

Four factors that are able to modify the DST results might explain this difference in DST results between the groups of two countries.

Firstly, the two groups show significant differences in their psychiatric family history with a higher rate of alcoholism in São Paulo and a higher rate of depression in Liège. Previous studies have demonstrated that NS depressive patients exhibited a lower incidence of alcoholism family history (Winokur *et al*, 1985; Zimmerman *et al*, 1986). Thus, this factor could explain, in part, the lower percentage of NS depressives in São Paulo.

Secondly, the number of previous depressive episodes is lower in São Paulo than in Liège. Previous reports have already found that DST NS shows a higher level of recurrence and a higher number of previous depressive episodes (Cohen and Lepine, 1988). Therefore, this factor might also explain the lower percentage of NS depressives in São Paulo.

Thirdly, only six patients in São Paulo were hospitalized as compared to the whole sample in Liège. Previous studies have described a higher rate of DST non-suppression among inpatients as compared to outpatients due to possible differences in clinical characteristics as well as to the stress of hospitalization (Coccaro *et al*, 1984). It should however be remembered that this effect of stress was observed within the first days following hospitalization; in our study DST was always performed at least 2 weeks after admission, suggesting that this factor could be negligible. Moreover, it is a fact that being treated as an outpatient in São Paulo is not associated with a lower severity of depressive illness, since the number of psychiatric beds in public hospitals is far below the needs. Brazilian politics encourages outpatient treatment for ideological and economic reasons.

Fourthly a factor that could have played a role is the use of oral contraceptives which are more frequent among Belgian women. A recent study, however, demonstrated a lack of significant influence of oral contraceptives in DST interpretation (Ansseau *et al*, 1993).

Besides, the difference in the socio-cultural level between the two groups could raise the issue of possible malnutrition in the São Paulo patients. In a study related to the use of the DST in a Brazilian hospital, the authors stressed the caution needed to interpret DST results in Brazil as well as in third world countries, due to the nutritional deficit (Kerr-Correa *et al*, 1990). It is important to emphasize that this factor was able to increase the percentage of DST NS in the São Paulo patients, while in our study, the Brazilian group shows a lower rate of NS depressives.

Finally, we can report to the Rihmer hypothesis concerning the role of latitude on DST results: Liège is located at 52° North latitude while São Paulo is located on the Tropic of Capricorn. Apart from many consequences of the location difference of these two cities, the effect of contrasted light/dark cycles and related melatonin secretion must be taken into account – Environmental lighting conditions influence melatonin secretion (Wetterberg, 1978; Lewy, 1984). Moreover, the disturbance of cortisol and melatonin rhythms may be interlinked as suggested by Wetterberg *et al* (1984). Indeed, these authors suggest that melatonin or some related factors produced by pineal may inhibit corticotrophin releasing factor. Thus, it can be hypothesized that a low melatonin level due to poor lighting conditions may be one of the causes for the elevated cortisol observed in NS depressive patients of the north part of Europe and the USA.

In conclusion, our study has shown a complexity of clinical, personal, familial factors and a geographic localization that could be related to the differences observed in the number of non-suppressors of DST between the Brazilian and Belgian samples. Future studies involving larger samples are needed to evaluate the respective roles of these variables more efficiently.

Acknowledgments

This research was supported by grants from Brazil and the French community of Belgium.

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