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**Original article**

# Clonidine test and MMPI scales in major depression: state or trait markers?

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**Summary** – The relationship between growth hormone (GH) response to clonidine and the Minnesota Multiphasic Personality Inventory (MMPI) was assessed in 20 major depressive inpatients. GH response to clonidine was negatively correlated with the depression, the psychasthenia as well as the social introversion MMPI scale scores, and positively correlated with the hypomania scale scores. In contrast, the Carroll depression scale did not exhibit any relationship with either GH response to clonidine or MMPI depression scale. These findings support the role of the clonidine test and several MMPI scales as trait markers for depressive illness.

**MMPI / clonidine test / major depression / Carroll depression scale**

## Introduction

A large number of studies have suggested decreased noradrenergic activity in depression, resulting from either a diminished neurotransmitter release or disturbances in the sensitivity of specific receptors (Willner, 1985).

Neuroendocrine strategy may provide an indirect index of central noradrenergic transmission. In particular, the growth hormone (GH) response to clonidine (an alpha-2 adrenergic agonist) is a well studied neuroendocrine test impaired in depression, especially endogenous subtypes (Matussek *et al,* 1980; Checkley *et al,* 1981; Charney *et al,* 1982; Siever *et al,* 1982; Siever and Uhde, 1984; Ansseau *et al,* 1988).

Post *et al* (1981) have related decreased noradrenergic function, assessed by plasma MHPG (a metabolite of noradrenaline), with depression, hypochondriasis, and psychasthenia in normal subjects using the well validated Minnesota multiphasic personality inventory (MMPI) (Graham, 1987). Thus, lower MHPG levels were associated with these three MMPI scales that would appear to represent the tendency for depressive mood, easy fatigability, and lack of energy and somatization. Unfortunately, this study did not include depressive patients.

The aim of the study was therefore to assess the relationship between noradrenergic function assessed by GH response to clonidine and MMPI scales among major depressive patients. The relationship between GH response and apomorphine test, a dopaminergic challenge, was previously reported (Pitchot *et al,* 1990-91).

## Methods

### *Subjects*

Our sample consisted of 20 patients hospitalized in the Psychiatric Unit of the University Hospital of Liège, Belgium. All patients fulfilled DSM III-R criteria for a major depressive disorder and had a minimal score of 20 on the Carroll self-rating scale for depression (Carroll *et al,* 1981) at the end of a drug-free period of at least two weeks. The patients were all unipolar and none of them exhibited psychotic features. The sample comprised 14 males and 6 females with ages ranging from 23 – 60 yrs (mean age = 43.0 yrs ± 10.0). Due to the influence of estrogen on GH release, postmenopausal females were excluded (Tulandi *et al,* 1987).

The patients were also controlled for medical illness by somatic history and medical examination, ECG, EEG, chest X-ray, and routine laboratory tests. They had also been free of drugs for at least two weeks at the time of the study and the clonidine test was always performed between the third and the twelfth days of the menstrual cycle in pre-menopausal females. Moreover, to be included, patients had to have a basal GH level of less than 5 ng/ml before clonidine challenge (Ansseau *et al,* 1984).

### *Neuroendocrine test procedure*

The clonidine challenge test was performed after an overnight fast. At 07 00 am, a butterfly needle was inserted in a forearm vein. Blood samples of 10 ml were collected 20 min before and immediately prior to the injection of clonidine at 08 00 am. Successive blood samples were collected at 20, 40, 60, and 120 min after clonidine injection. Clonidine 0.15 mg diluted in saline to obtain 20 ml, was injected intravenously over a period of 10 min. Patients were aware of the time and duration of clonidine injection.

GH was measured with a double antibody radioimmunoassay (Franchimont, 1968), with intra- and inter-assay coefficients of variation of respectively 13.3 ± 4.7 % and 14.8 ± 9.6 % and a detection limit of 0.2 ng/ml. A blunted GH response to clonidine was defined by a GH peak lower than 5 ng/ml (Ansseau *et al,* 1984).

### *Personality inventory procedure*

Automated MMPI (Lewi and Pinchard, 1967) was completed by the patients within two days of the clonidine test. According to the usual methodologies, MMPI profiles with scores on the F (rare endorsement), and K (correction) validity scales higher than 70 were rejected as well as an F-K index higher than 12 (Graham, 1987).

### *Data analysis*

GH response to clonidine was assessed by the area under the curve situated between injection (t0) and the last blood sampling (t120). Analysis was performed using absolute GH values as well as differences related to basal levels (relative values). Since the correlation between absolute and relative values was very high ($r > 0.98$), only the absolute values are reported here.

Since data were unimodally distributed, the relationship between MMPI scale scores and GH response to clonidine was assessed by Pearson's correlation coefficients, while MMPI scores between blunted and normal responders to the clonidine test were compared using the *t*-test. Pearson's correlation was preferred over the Spearman's correlation since MMPI scores are generally considered as numeric variables.

## Results

Blunted GH responses to clonidine were observed in 11 patients (55%). Age, as well as gender distribution, did not significantly differ between patients with normal or blunted GH response (respectively 43.1 yrs ± 12.5 *vs* 43.0 yrs ± 8.2, t = 0.001, $P = 0.98$, and 8 males and 3 females *vs* 6 males and 3 females, $\chi^2 = 0.038$, df = 1, $P = 0.84$).

Pearson's correlation coefficients between GH responses to clonidine and MMPI scale scores are presented in table I. GH response was positively correlated with the hypomania scale scores ($P = 0.04$), and negatively with the depression ($P = 0.02$), psychasthenia ($P = 0.015$), as well as social introversion scale scores ($P = 0.05$). However, no significant differences were found between blunted and normal responders to clonidine on these four MMPI scales (depression: F 1,18 = 2.94, $P = 0.10$; psychasthenia: F 1,18 = 4.27 = 0.055; hypomania: F 1,18 = 2.50, $P = 0.13$; social introversion: F 1,18 = 2.10, $P = 0.16$) (table II).

In contrast, scores on the Carroll self-rating scale for depression were not correlated with either GH response to clonidine ($r = 0.20$, df = 19, $P = 0.39$), or MMPI depression scale ($r = 0.28$, df = 19, $P = 0.23$).

**Table I.** Pearson's correlation coefficients between GH response to clonidine and MMPI scale scores in 20 major depressive inpatients (df = 19).

| *MMPI scales* | | *r* | *P* |
|---|---|---|---|
| IN | (indecision) | 0.13 | 0.59 |
| L | (lie) | 0.13 | 0.59 |
| F | (rare endorsement) | 0.11 | 0.64 |
| K | (correction) | − 0.27 | 0.24 |
| HS | (hypochondriasis) | 0.02 | 0.94 |
| D | (depression) | − 0.52 | 0.02 |
| HY | (hysteria) | − 0.13 | 0.59 |
| PD | (psychopathic deviate) | − 0.32 | 0.16 |
| MF | (masculinity-femininity) | 0.03 | 0.91 |
| PA | (paranoia) | − 0.20 | 0.39 |
| PT | (psychasthenia) | − 0.53 | 0.01 |
| SC | (schizophrenia) | − 0.10 | 0.67 |
| MA | (hypomania) | 0.47 | 0.04 |
| SI | (social introversion) | − 0.44 | 0.05 |
| AT | (anxiety) | − 0.11 | 0.62 |
| ES | (ego strength) | 0.32 | 0.17 |

**Table II.** Comparison of MMPI subscales scores (mean and SD) between blunted and normal responders to clonidine test.

| *MMPI subscales* | *Blunted (n = 11)* | *Normal (n = 9)* | *t* | *P* |
|---|---|---|---|---|
| IN (indecision) | 52.6 ± 2.4 | 53.7 ± 2.6 | 1.05 | 0.31 |
| L (lie) | 53.6 ± 7.6 | 55.6 ± 7.5 | 0.31 | 0.58 |
| F (rare endorsement) | 52.3 ± 9.7 | 57.0 ± 9.5 | 1.07 | 0.31 |
| K (correction) | 51.9 ± 6.2 | 47.8 ± 7.1 | 2.20 | 0.15 |
| HS (hypochondriasis) | 63.3 ± 9.5 | 63.6 ± 10.2 | 0.01 | 0.95 |
| D (depression | 85.7 ± 14.3 | 75.2 ± 13.2 | 2.94 | 0.10 |
| HY (hysteria) | 67.8 ± 11.5 | 67.1 ± 10.2 | 0.02 | 0.88 |
| PD (psychopathic deviate) | 67.2 ± 11.0 | 61.5 ± 11.2 | 1.35 | 0.25 |
| MF (masculinity-femininity) | 53.0 ± 8.9 | 53.4 ± 10.2 | 0.01 | 0.92 |
| PA (paranoia) | 64.3 ± 11.6 | 60.5 ± 11.5 | 0.51 | 0.48 |
| PT (psychasthenia) | 78.3 ± 13.5 | 67.4 ± 12.7 | 4.27 | 0.05 |
| SC (schizophrenia) | 72.5 ± 13.6 | 70.2 ± 14.2 | 0.13 | 0.71 |
| MA (hypomania) | 50.7 ± 12.5 | 58.6 ± 11.6 | 2.49 | 0.13 |
| SI (social introversion) | 64.3 ± 12.7 | 56.2 ± 10.9 | 2.10 | 0.16 |
| AT (anxiety) | 66.9 ± 9.7 | 65.6 ± 8.7 | 0.09 | 0.76 |
| ES (ego strength) | 34.9 ± 11.7 | 38.8 ± 10.8 | 0.61 | 0.44 |

## Discussion

The results of this study show an association between GH response to clonidine and MMPI scale scores in major depressive patients. GH response is negatively correlated with depression, psychasthenia, and social introversion MMPI scales, and positively correlated with the hypomania scale. Such a profile is related to depressed mood, lack of energy, and diminished interests. Thus, noradrenergic disturbances, especially subsensitivity of alpha-2 adrenergic receptors, are associated with a particular profile on MMPI. However, the lack of a control group in the present study makes it impossible to address the issue of the specificity of our findings in major depression. However, similar results (altered noradrenergic function and MMPI profile) were reported by Post *et al* (1981) in normal subjects.

In the past, a large number of studies have attempted to relate another biological marker of depression, the dexamethasone suppression test (DST), and MMPI scales with controversial results. No difference in MMPI scores have been reported between suppressor and non-suppressor patients in two studies (Stokes *et al,* 1976; Norman *et al,* 1985). In contrast, Szaboczky *et al* (1983) have reported elevated scores on the hypomania, depression, hypochondriasis, and schizophrenia scales in DST non-suppressor patients. Moreover, in a recent study of Ansseau *et al* (1986), cortisol levels following DST were positively correlated with the depression as well as the social introversion MMPI scales, and negatively with the hypomania scale. These latter results are very similar to those of the present study. Thus, the same MMPI profile seems to be associated with disturbances in two different biological markers of depression. This similarity can be interpreted on the basis that noradrenergic input inhibits the hypothalamic-pituitary-adrenal (HPA) axis (Hillhouse *et al,* 1975). Thus, in depression, decreased noradrenergic activity could be associated with increased cortisol secretion (Siever and Uhde, 1984). However, other neurotransmitters, such as acetylcholine or serotonin, may also contribute to the hypercortisolemia noted in depressive disorders.

An interesting finding of the present study concerns the opposite correlation between GH response to clonidine and the depression and hypomania scales. Negative correlations between hypomania scale scores and post DST cortisol levels have been reported previously (Bryer *et al,* 1983; Ansseau *et al,* 1986). Our results suggest that the clonidine test is also related to the depressive/mania psychopathological dimension. These findings are in agreement with the noradrenergic hyperactivity hypothesis in mania, based on higher urinary levels of MHPG in the manic phase in comparison with the depressive phase, and on indirect pharmacological data suggesting that drugs which decrease noradrenergic function such as reserpine exacerbate depression but improve mania, while drugs which stimulate the noradrenergic system improve depression and aggravate manic symptoms (Post, 1980). However, the noradrenergic hyperactivity hypothesis is not sup-

ported by the blunted GH response to clonidine reported in mania (Ansseau *et al,* 1987).

The relationship between the clonidine test and severity of depressive symptomatology was never specifically assessed previously. Our finding of a lack of correlation between the Carroll self-rating scale for depression and GH response to clonidine was similar with those relating MHPG with the severity of depression (Beckman and Goodin, 1980; Agren, 1982).

In fact, several studies have shown that GH response to clonidine remains blunted after clinical recovery (Siever and Uhde, 1984; Mitchell *et al,* 1988). Moreover, we previously demonstrated the lack of relationship between disturbances in the clonidine test and the level of life events preceding hospitalization in depressive patients (Ansseau *et al,* 1990). The clonidine test could therefore be considered as a "trait marker" of depression, whereas scores on depression rating scales, fluctuating easily with the current mood, represent more a "state marker". Overall, the intensity of depressive symptomatology, assessed by the Carroll rating scale for depression, does not appear to be related to alpha-2 adrenergic disturbances.

The role of MMPI as a state or trait variable is still a subject of controversy (Graham, 1987). Initially developed as a measure of personality traits and therefore considered as a stable individual characteristic, the MMPI has been shown to be influenced by various conditions, at least with regard to several subscales (Graham, 1987). The results of our study suggest that the depression, psychasthenia, hypomania and social introversion subscales could represent 'trait' markers, since they exhibit significant correlations with a 'trait' biological parameter.

In conclusion, this study supports an association between the clonidine test and personality traits related to the depressive/manic dimension. This finding should however be considered as preliminary due to the rather small sample of patients and should be confirmed in further studies.

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