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Brief report

Neopterin levels and dexamethasone suppression test in obsessive–compulsive disorder

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Abstract

Neopterin, a biopterin precursor that is released by macrophages, is an important immunological marker in psychiatric disorders. It has been reported that glucocorticoids may cause suppression of cell-mediated immunity and consequently result in decreased neopterin levels. In the present study, we evaluated whether dexamethasone suppression test (DST) and neopterin findings were associated with pure obsessive–compulsive disorder (OCD) patients (OCD-D group) and the concomitant OCD and depression (OCD+D group). The sample comprised 44 patients with OCD (27 with OCD-D and 17 with OCD+D) and 30 control subjects. There was significantly higher DST nonsuppression in the OCD+D group than in the OCD-D group. With regard to mean neopterin levels, there was no significant difference between the OCD-D group and the control group, but there was a statistically significant difference between the OCD+D group and the control group. The OCD+D group had significantly lower neopterin levels than the 20 OCD-D group. We suggest that this distinction may reflect the fact that glucocorticoids can lead to suppression of cell-mediated immunity and consequently can result in decreased neopterin levels. In conclusion, our results suggest that not the OCD-D group had normal neopterin levels and DST results, and also that OCD may be a heterogeneous subtype characterized by some biological indicators or anxiety and affective disorders.

Keywords: OCD; Neopterin; DST; Depression

1. Introduction

Obsessive–compulsive disorder (OCD), which is classified as an anxiety disorder in DSM-IV, is frequently accompanied by depressive symptoms and comorbid depressive disorder (Jenike, 1983; Marks, 1983). On the other hand, obsessions and compulsions may be found in patients with depressive disorders (Goodwin et al., 1969). This relationship has resulted in increased research into the biological association of OCD and affective disorders.

The dexamethasone suppression test (DST), which is used in the diagnosis of Cushing syndrome, is a specific and sensitive diagnostic test for depressive disorder

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(Carroll et al., 1981). However, because of the fact that DST nonsuppression has been observed in a variety of organic and psychiatric disorders, its use and specificity have remained unclear (Checkley, 1985). The comorbidity of OCD and depressive disorder is a finding that is frequently observed. While patients with OCD have an approximate 80% rate of secondary depression, 30% of patients with depressive disorder have obsessive–compulsive symptoms (Nemiah and Uhde, 1989). Jenike et al. (1987) found that four of five (80%) patients with comorbid OCD and depression amongst 29 OCD patients had normal DST findings and that none of the patients without comorbid depression exhibited DST nonsuppresion. Monteiro et al. (1986) examined 61 OCD patients and found that 9 of 11 patients with comorbid depression had DST nonsupression whereas only 2 out of 50 patients with pure OCD had DST nonsuppression. In another study (Lieberman et al., 1985) in which patients with OCD and major depressive disorder were compared, the patients with OCD had either pure OCD or minimal affective symptomatology, and none of them exhibited DST nonsuppression. In the same study, it was determined that 7% of patients with major depressive disorder had abnormal DST findings. Catapano et al. (1990) evaluated 18 OCD patients without depression and reported that five (27.7%) of the patients had DST nonsuppression. Gehris et al. (1990) reported that OCD patients in their study had significantly higher free cortisol levels than healthy controls at initial examination but that their cortisol levels normalized after 10 weeks of clomipramine treatment. In a study performed in 16 patients with OCD, Insel et al. 1985 reported that six (37%) of the patients had DST nonsuppression, and five of the six had scores above 20 on the Hamilton Depression Rating Scale (HDRS). In another study (Cottraux et al., 1984), it was found that 30% of patients with OCD were DST nonsuppressors but did not differ significantly from DST suppressors on HDRS scores.

Recently, neopterin, which is a biopterin precursor released by macrophages, has assumed growing importance as an immunological marker in psychiatric disorders (Huber et al., 1984; O'Hanlon et al., 1996; Korte et al., 1998). In a study performed by Maes et al. (1994), moderately increased neopterin plasma levels were found in melancholic depressive patients compared with normal healthy subjects, and it was suggested that severe depression might be an immune response. It is produced by activation of cyclohydrolase, which is stimulated by interferon-γ (INF-γ). It has been accepted as an important indicator of the cellular immune system because INF-γ is released by T-lymphocytes (Huber et al., 1984; Besedovsky et al., 1986). However, the cell types related to humoral immunity (e.g. B-lymphocytes) do not release measurable levels of neopterin (Huber et al., 1984). It was reported that glucocorticoids could cause suppression of cell-mediated immunity and consequently could result in decreased neopterin levels. To the best of our knowledge, there is no study of neopterin levels in adult patients with OCD. For this reason, we decided to evaluate the following factors: (1) whether the DST was associated with pure OCD, (2) whether the DST was associated with OCD and comorbid depression, and (3) whether neopterin levels were affected by pure OCD and the comorbidity of OCD and depression.

2. Methods

2.1. Subjects

The study group consisted of 44 patients (27 females, 17 males) who were admitted to the Psychiatry Department of Fýrat University Medical Faculty as inpatients ($n=18$, 40.9%) or outpatients ($n=26$, 59.1%) and diagnosed as OCD according to DSM-IV. A semi-structured interview was carried out in order to establish DSM-IV diagnosis. Of these patients, 17 had comorbid depressive disorder (15 major depressive disorder, 2 dysthymic disorder) according to DSM-IV. After a period of 2 weeks free of medication, all patients underwent physical examination, total biochemistrical evaluation, chest X-ray, urinalysis and ECG. Exclusion criteria were as follows: history of any endocrinological condition, gestation, obesity, alcohol abuse and dependence, recent or present infection, history of immunologic disease and taking any prescription drug. After complete description of the study to the subjects, written informed consent was obtained from each patient and control. Additionally, the approval of the local ethical committee was obtained. Female subjects were tested in different menstrual phases.

2.2. Controls

The control group was composed of healthy subjects ($n=30$) who applied to the Psychiatry Department of Fýrat University Medical Faculty for a driving license examination and were evaluated as normal. Exclusion criteria were as follows: history of any endocrinologic condition, gestation, obesity, alcohol abuse and dependence, history of recent or present infection, history of immunologic disease and oral contraceptive use. Healthy subjects were evaluated in a detailed clinical interview to exclude DSM-IV psychiatric disorders.

2.3. DST procedure

Blood samples for the determination of cortisol were taken from all subjects at 08.00 h after fasting, not drinking alcohol and coffee and not smoking for 12 h since blood was drawn on the first day. Blood samples after a 1-h rest period were drawn in a comfortable area to control tension. A cannula was inserted into a forearm vein, and blood was drawn 45 min after inserting the cannula. The serum cortisol level was measured using a commercially available kit (Immulite 2000 cortisol, Diagnostic Products Corporation, Los Angeles, CA, USA) with a chemiluminoassay method. On the same day at 23.00 h, 1 mg dexamethasone was administered. The cortisol levels were determined on the following day at 16.00 h again. Procedures established by Carroll et al. (1981) were strictly followed, the cutoff point for nonsuppression being 5 μg/dl. Intra- and inter-assay coefficients of variation were <6.1% and 7.8%, and sensitivity was 0.20 μg/dl.

2.4. Neopterin procedure

The procedure was the same as for cortisol. Blood samples were taken from the cases into dry tubes at 8.00 h on the first day, and the sera were collected by centrifuging the tubes at 250 ×*g*. The sera were stored at 20 °C in deep-freeze to be assessed for neopterin levels. Serum neopterin levels of the subjects were measured by the ELISA (enzyme linked immunoassay) method (Neopterin; BRAHMS Diagnostica GmbH, 16761 Berlin, Germany).

2.5. Instruments

2.5.1. Sociodemographic information form

All subjects were evaluated by a semi-structured questionnaire form which was arranged in accordance with clinical experience and available information sources and included gender, age, marital status, educational condition, socieconomic status, duration of illness.

2.5.2. Hamilton Depression Rating Scale

The 17-item HDRS (Hamilton, 1960) is used to rate the severity of depression. An HDRS score above 25 is considered to indicate significantly severe depression, whereas scores of 18 to 24 are severe, 7 to 17 moderate, and 7 or below as no depression.

2.5.3. Yale–Brown Obsessive–Compulsive Scale (Y-BOCS)

The Y-BOCS (Goodman et al., 1989) is used to assess the severity of OCD without focusing on the contents of obsession and compulsion. It has 10 items. Each one is assessed by a clinician on a scale of 1 to 4.

2.6. Statistical analysis

The data were evaluated with SPSS for Windows 9.0 (SPSS/PC, 1998). Comparisons were performed by Mann–Whitney–*U* tests and Kruskal–Wallis tests (for two-group comparisons by the former and for all group comparisons by the latter) and by Wilcoxon tests (for the comparisons of basal and postdexamethasone cortisol levels within groups). For correlation evaluations, the Spearman correlation test (two-tailed) was used. $P<0.05$ was considered to be significant.

3. Results

3.1. Sociodemographic characteristics

A total of 44 patients (27 females and 17 males) were enrolled in this study. The control group ($n=30$) consisted of 18 (60%) females and 12 (40%) males. The mean age was 28.18±4.90 (range = 18–49) for the patient group and 26.50±6.58 for the controls (range = 19–47), respectively. Of the patients, 13 (29.5%) were treated as inpatients and 31 (70.5%) as outpatients (Table 1).

Table 1
Demographic and clinical features of the patients and the controls*

Total patients: 44
Sex: males 17 (38.6%); females 27 (61.4%)
Age: 28.18±4.90 (range = 18–49)
Inpatients 13 (29.5%); Outpatients 31 (70.5%)
Subgroups
OCD+D group: 17 (38.6%)
OCD-D group: 27 (61.4%)
Scale scores
HDRS score: 11.00±9.20
Y-BOCS score: 24.47±7.39
According to HDRS:
Moderate depression 7 (15.9%)
Severe depression 10 (22.7%)
According to Y-BOCS:
Mild OCD 5 (11.4%);
Moderate OCD 13 (29.5%)
Severe OCD 19 (43.2%);
Significantly severe OCD 7 (15.9%)
Control group: 30
Sex: males 12 (40%); females 18 (60%)
Age: 26.50±6.58 (range = 19–47)

*Values are presented as mean (S.D.) (for continuous variables) and as numerical (%) (for nominal variables).

3.2. Scale scores

The mean HDRS score of the patient group was 11.00±9.20. There were 7 patients (15.9%) with moderate depression and 10 patients (22.7%) with severe depression (Table 1).

Five patients (11.4%) with mild OCD, 13 (29.5%) with moderate OCD, 19 (43.2%) with severe and 7 patients (15.9%) with significantly severe OCD were determined by Y-BOCS (Table 1).

The patients were divided into two subgroups according to the presence or absence of comorbid depression; OCD+D group (for OCD and comorbid depressed patients) and OCD-D group (for pure OCD patients).

3.3. DST results

The mean basal cortisol levels were 12.54±3.80 μg/dl in the OCD+D group, 8.81±2.74 μg/dl in the OCD-D group, and 12.44±3.32 in control group, respectively (df=2, P<0.001). The mean postdexamethasone cortisol levels were 4.61±2.37 μg/dl in the OCD+D group, 2.03±1.01 μg/dl in the OCD-D group, and 2.50±1.32 in the control group, respectively (df=2, P<0.01). In all groups, there was a statistically significant difference between basal and postdexamethasone cortisol levels (df=1, P<0.001 for each group). While, 12 (70.6%) of 17 patients in the OCD+D group had DST nonsuppression, none of the OCD-D patients had DST nonsuppression (χ^2=17.8, P<0.00002) (Table 2).

Two of five patients with mild OCD according to the Y-BOCS were DST nonsuppressor. Four of 13 patients with moderate OCD, and five of 19 patients with severe OCD had DST nonsuppression. One of seven patients with significantly severe OCD exhibited DST nonsuppression (χ^2=0.873, df=3, P=0.832).

Table 2
Basal cortisol, postdexamethasone cortisol and neopterin levels in all groups

Groups	Basal cortisol (μg/dl)	Postdexamethasone cortisol (μg/dl)	Neopterin (nmol/l)
I. OCD+D group (n=17)	12.54±3.80	4.61±2.37	3.47±0.72
II. OCD-D group (n=27)	8.81±2.74	2.03±1.01	6.67±1.54
III. Control group (n=30)	12.44±3.32	2.50±1.32	6.88±2.00
I–II–III *	χ^2=16.301, P<0.001	χ^2=13.308, P<0.01	χ^2=38.711, P<0.001
I–II **	0.002	0.001	0.0001
I–III **	n.s.	0.002	0.0001
II–III **	0.0001	n.s.	n.s.

n.s., Not significant.
* Kruskal–Wallis test.
** Mann–Whitney U test.

Table 3
Correlations between cortisol values, neopterin values, age, and scale scores in all groups

	OCD+D group			OCD-D group			Control group		
	BC	PC	N	BC	PC	N	BC	PC	N
BC	–	0.75[a]	−0.60[b]	–	0.73[a]	n.c.	–	n.c.	n.c.
PC	–	–	−0.74[a]	–	–	n.c.	–	–	n.c
Age	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.
HDRS	−0.92[a]	−0.66[a]	−0.50[b]	n.c.	n.c.	n.c.	–	–	–
Y-BOCS	n.c.	n.c.	n.c.	n.c.	n.c.	n.c.	–	–	–

BC, basal cortisol; PC, postdexamethasone cortisol; N, neopterin.
[a]P<0.01, [b]P<0.05.
n.c., no correlation.

There was a direct correlation between basal cortisol and postdexamethasone cortisol in all groups (r=0.75, P<0.01 for the OCD+D group; r=0.73, P<0.01 for the OCD-D group) except for the control group (r=0.022, P>0.05). There was no correlation between age and the Y-BOCS (r=0.011, P>0.05) and basal cortisol (r=0.034, P>0.05) and postdexamethasone cortisol (r=0.038, P>0.05). There was no correlation between the HDRS and basal (r=0.039, P>0.05) and postdexamethasone cortisol (r=0.021, P>0.05) in the OCD-D group whereas the HDRS showed a direct correlation with basal (r=−0.92, P<0.01) and postdexamethasone cortisol (r=−0.66, P<0.01) in the OCD+D group (Table 3).

3.4. Neopterin results

While the mean neopterin level in the OCD+D group was 3.47±0.72 nmol/l, the OCD-D group had a mean

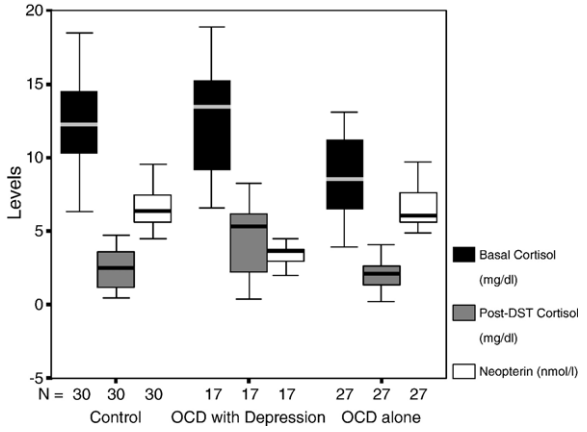

Fig. 1. Boxplot of basal and postdexamethasone cortisol and neopterin levels in each group.

level of 6.67±1.54 nmol/l, whereas it was 6.88±2.00 in the control group (df=2, P<0.001). No significant difference in mean neopterin level was found between the OCD-D group and the control group, while we found statistically significant higher levels in the OCD+D group than in the control group (df=1, P<0.001) (Table 2).

No statistically significant correlation between neopterin levels and basal cortisol (r=0.226, P>0.05), postdexamethasone cortisol (r=0.232, P>0.05), age (r=0.226, P>0.05), HDRS (r=0.026, P>0.05) and Y-BOCS (r=0.038, P>0.05) was found in the OCD-D group. In the OCD+D group, there was a significant negative correlation with basal and postdexamethasone cortisol and the HDRS score (r=−0.60, P<0.05; r=−0.74, P<0.01; r=−0.50, P<0.05, respectively) (Table 3).

The distribution of basal cortisol, postdexamethasone cortisol and neopterin levels in all groups (formed boxplot) is presented in Fig. 1.

4. Discussion

The results of studies of neopterin levels in psychiatric patients have been inconsistent. In a study that compared patients with alcohol dependence to healthy controls with regard to neopterin levels, O'Hanlon et al. found lower levels of neopterin in the patient group than in controls, and they proposed that this finding might be related to the suppression of macrophage function (O'Hanlon et al., 1996). In addition, it was suggested that there was a relationship between excessive alcohol intake and adrenocortical overactivity and hypercortisolism (Mendelson et al., 1971; Stokes, 1973) and that glucocorticoids could suppress the function of monocytes and macrophages (Crabtree et al., 1979). O'Toole et al. (1998) reported a slight suppression of neopterin levels in depressed patients compared with matched controls. They suggested that neopterin might not be a useful indicator for the severity and the duration of a depressive episode. Korte et al. (1998) evaluated the neopterin levels of 29 inpatients with acute schizophrenia and reported significantly higher levels of neopterin in the patients compared with controls, especially in patients who had shown clinical improvement. They suggested that this increase might be related to up-regulation of dopamine turnover, because neopterin is the first intermediate in the synthesis of tetrahydrobiopterin that is a co-factor in the activation of tyrosine hydroxilase. In our style, the mean neopterin level was 3.47±0.72 ng/ml in the OCD+D group whereas it was 6.67±1.54 ng/ml in the remaining patients (i.e., in the OCD-D group). No statistically significant correlation was determined between the severity of OCD and neopterin level.

In the present study, the mean postdexamethasone cortisol level was 3.03±2.08 μg/dl in the total group of patients. This level was higher compared with the level of 1.47±1.5 μg/dl which was found by Lieberman et al. (1985) in patients with OCD. However, the fact that OCD patients had minimal affective symptomatology in that study may explain the difference between the two studies.

In our study, no significant correlation was found between the severity of OCD and DST nonsuppression. There are relatively few studies that examined the association between the DST and the severity of OCD in the literature. In one study, Insel et al. (1985) suggested that an observed association between the severity of OCD and DST nonsuppression might reflect the fact that OCD inpatients had stronger findings than outpatients. In contrast, no correlation between postdexamethasone cortisol levels and OCD severity was found in another study (Coryell et al., 1989). Our results are in agreement with the results of the majority of the studies (Lieberman et al., 1985; Jenike et al.,1987; Monteiro et al., 1986). We suggest that the finding of no association between DST nonsuppression and the severity of OCD casts doubt upon the specificity and sensitivity of the DST in OCD.

To our knowledge, this is the first study of neopterin levels in patients with OCD. Therefore, we wanted to emphasize some findings from the present study in order to light the way for new researches: (1) The DST is neither a specific nor a sensitive test for pure OCD. However, there is a condition that is characterized by significant nonsuppression in the patients with comorbid depression. (2) The patients with OCD and comorbid depression have significantly lower neopterin levels compared with the patients with pure OCD. We suggest that this distinction may be associated with the fact that glucocorticoids can cause suppression of cell-mediated immunity and consequently can result in decreased neopterin levels. There are few studies examining the immune system in patients with OCD. Brambilla et al. (1997) found OCD patients without depression to have lower plasma interleukin-1β (Il-1β) and tumor necrosis factor-α (TNF-α). They reported that norepinephrine and hypothalamic–pituitary–adrenal axis activity, which have been reported to be increased in OCD, might lead to the inhibition of cytokine secretion. Thus, since neopterin has been accepted as an important indicator of the cellular immune system, it may be expected that neopterin levels in OCD may

decrease (Huber et al., 1984; Besedovsky et al., 1986). However, in our study, the patients with comorbid OCD and depression seem to have, whereas pure OCD patients do not have, hyperactivity of the hypothalamic–pituitary–adrenal axis based on their DST results. Both parameters (DST and neopterin) are associated with OCD in cases that are comorbid with depressive disorder. Our results suggest that pure OCD patients have normal neopterin levels and also are not non-suppressors on the DST. OCD may be a heterogeneous group including some biological indications of anxiety and affective disorders. However, more comprehensive and detailed studies must be performed in order to decipher the exact role of neopterin in OCD.

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