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ORIGINAL PAPER

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Neopterin production in posttraumatic stress disorder before and after pharmacotherapy

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Abstract Post-traumatic stress disorder (PTSD) has been associated with decreased neopterin levels. In the present study, we evaluated whether this low neopterin levels would normalize following pharmacotherapy with sertraline in PTSD. Fourteen patients with PTSD and 14 controls were enrolled in the study. A clinical evaluation and measurements of neopterin levels before and after sertraline treatment were performed. In addition, all patients were assessed with the Clinician Administered PTSD Scale (CAPS). The mean neopterin levels were significantly lower in the patient group than control group at baseline and were negatively correlated with the duration of illness, or severity of illness. Sertraline treatment decreased the symptoms of PTSD; however this was not accompanied by a significant increase in neopterin production. In conclusion, our results reveal that the failure for neopterin to normalize through symptom alleviation suggests that either neopterin may be a trait marker of the illness, or that more sustained treatment is necessary to elevate the neopterin production.

Key words PTSD · neopterin · sertraline · CAPS

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Introduction

Neopterin, a biopterin precursor released by macrophages has recently gained growing importance in psychiatric disorders (O'Hanlon et al. 1996; Korte et al. 1998; Atmaca et al. in press). It has been accepted as an important indicator of cellular immune system (Besedovsky et al. 1986). However, the cell types related to humoral immunity (e. g., B-lymphocytes) do not release the measurable level of neopterin (Huber et al. 1984). In addition, neopterin is a by-product in the synthesis of tetrahydrobiopterin which is a cofactor of tyrosine hydroxylase, an essential enzyme in catecholamine neurotransmitter synthesis (Wachter et al. 1989). Controversial results have been reported in the trials evaluating neopterin in psychiatric patients (Maes et al. 1994; O'Toole et al. 1998; Korte et al. 1998).

Post-traumatic stress disorder (PTSD), a stress reaction with a high rate of comorbidity (Maes et al. 2000; Grabe et al. 2000), is classified under anxiety disorders in DSM-IV (APA 1994). However, trauma alone is not enough to explain the occurrence of PTSD because many people experience a traumatic stressor but few develop PTSD. Probable post-traumatic biological factors seem to be effective on the development of PTSD. Stressor-related autonomic hyperactivity and changing the activity of hypothalamo-pituitary-adrenal (HPA) axis have been established in PTSD. HPA axis is obviously sensitive to stress-related disorders. It was reported that glucocorticoids (the last product of HPA axis) could cause suppression of cell-mediated immunity and consequently could cause reduction in neopterin levels. In our previous study, we have suggested that PTSD may be associated with neopterin (Atmaca et al. in press). In the present investigation, we sought to determine whether the decreased neopterin levels observed in patients with PTSD would be restored with alleviation of symptoms after sertraline treatment.

Methods

Subjects

A total of 28 subjects were recruited to the present study, comprising 14 patients (8 females, 6 males) with a mean age of 32.5 ± 5.3 years (range 18–41) who had applied to Firat University School of Medicine Department of Psychiatry and diagnosed with PTSD according to DSM-III-R, and 14 age- and sex-matched healthy controls. These subjects were those of our previous study (Atmaca et al. 2002). Written consent to participate in the study was obtained from the subjects after they were thoroughly informed about the research details. The research protocol was approved by the F[i]rat University School of Medicine Ethics Committee.

Female subjects were tested in the different menstrual phases. The vast majority of those were in early follicular phase (n = 6), and remainings in late luteal phase. Each patient underwent diagnostic evaluation by one trained psychiatrist using the Structured Interview for DSM-III-R Outpatient Form (SCID-OP) (Spitzer et al. 1987). The patients with any kind of axis I comorbidity were excluded. In addition, all subjects were evaluated by the Clinician Administered PTSD Scale (CAPS) (Blake et al. 1990), adapted for Turkish patients with established validity and reliability (Aker et al. 1999). CAPS is a widely used instrument in the assessment of PTSD.

A total of 14 healthy control subjects (mean age = 29.9 ± 6.1 years; range 21–44) according to exclusion criteria were chosen from the hospital staff. Controls were interviewed with the SCID (SCID-NP) to exclude any axis I disorder (Spitzer et al. 1990).

All patients underwent physical examination, total biochemistry evaluation, chest X-ray, urinalysis and ECG. All participants were carefully assessed to rule out autoimmune, pulmonary, infectious diseases and neoplasms. Exclusion criteria were the history of any endocrinological condition, gestation, obesity, alcohol abuse and dependence, recent or present infection, the history of immunologic disease and oral contraceptive use.

Procedures

All subjects were free of all medications at least two weeks prior to baseline blood sampling. The patients received sertraline. The initial dose of sertraline was 50 mg, with 50 mg increments occurring every 2 weeks, to a maximum dose of 200 mg, as determined by treatment response and side effects (range, 100–200 mg), with the mean daily dose of 132.1 ± 46.6 mg/day. The medications were received each morning after breakfast. The only concurrent medication permitted was alprazolam. Blood sampling from patients as well as from healthy controls was carried out on the initial test day and after 8 weeks of treatment only in the patients. Blood samples were taken from the subjects into dry tubes at 8.00 a. m. The sera were collected by centrifuging the tubes at 250 x *g*. The sera were stored at –20 °C until assessment of neopterin levels. Serum neopterin levels of the subjects were measured by the ELISA (enzyme linked immunoassay) method (Neopterin; BRAHMS Diagnostica GmbH, 16761 Berlin, Germany).

Statistical analysis

Obtained data were evaluated by SPSS for windows 9.0 (SPSS, 1998). The comparisons within the patient group throughout the study were performed by using the paired *t* test, whereas those between intergroups were carried out by using the independent samples *t* test. The chi-square test was used to compare categorical variables between groups. For correlation evaluations, the Spearman correlation (two-tailed) test was used. $p < 0.05$ was considered to be significant.

Results

Only one patient did not continue in the study through to week 3 due to an adverse event. Age and female/male ratio did not differ between groups significantly ($p > 0.05$). The mean CAPS score of the patient group was 52.5 ± 19.5 at baseline. The mean duration of illness for the patient group was 3.6 ± 2.6 years.

First of all, sertraline treatment attenuated the symptoms of PTSD. CAPS scores declined significantly over the 8 weeks of sertraline treatment (from the mean of 52.5 ± 19.5 to 29.4 ± 8.9; $p < 0.05$); however this was not accompanied by a significant increase in neopterin production. The mean baseline neopterin level was significantly lower in the patients compared with healthy controls (4.3 ± 1.1 vs. 8.0 ± 2.1 nmol/ml, respectively). A significant difference between the patient and control groups was found ($p < 0.001$). However, there were no significant differences in either of the two groups between mean values for men and women (patients: men = 4.7 ± 1.4 vs. women = 4.1 ± 1.0 nmol/ml; controls: men = 8.6 ± 2.3 vs. women = 7.8 ± 1.9 nmol/ml).

There were significant correlations between baseline neopterin levels and the duration of illness (r = –0.37, $p < 0.05$) or CAPS scores (r = –0.43, $p < 0.05$). No significant correlation was found between decrease in CAPS scores and increase in neopterin levels (r = –0.06, $p > 0.05$).

The baseline and post-treatment neopterin levels for groups are presented in Fig. 1.

Discussion

This study demonstrates that the patients with PTSD have statistically significant lower neopterin levels compared to controls and that there are statistically significant correlations between baseline neopterin levels and the duration of illness, or CAPS scores. However, the present study fails to demonstrate any alteration in the production of neopterin through sertraline treatment.

The studies regarding neopterin in psychiatric disorders have reported controversial results. O'Toole et al.

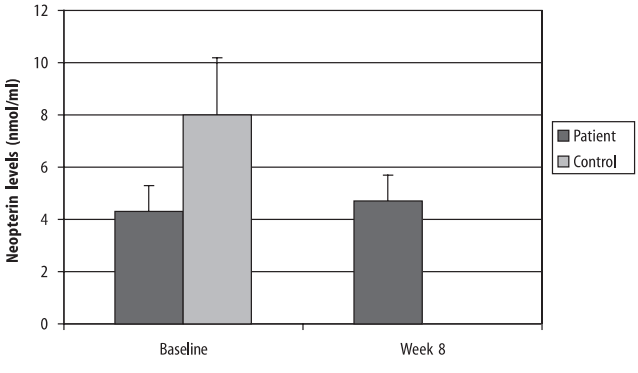

Fig. 1 The baseline and post-treatment neopterin levels in groups

(1998) 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 in-patients with acute schizophrenia and reported that patients especially with clinical improvement had significantly higher levels of neopterin compared to controls. In our study, baseline neopterin levels in patients with PTSD were decreased compared with the control group. Several mechanisms can be proposed to explain these findings. First, PTSD seems to be characterized by increased basal and postdexamethasone cortisol levels (Atmaca et al. in press). This might have caused the suppression of T-cells because of the fact that glucocorticoids could suppress the cell-mediated immunity and consequently could lead to reduced neopterin levels. These results are in conflict with research that demonstrated lower baseline plasma cortisol levels, lower mean 24-hour urinary cortisol excretion and a series of alterations that are distinct from those reported in major depressive disorder and have concluded that cortisol nonsuppression is rare in PTSD unless there is concomitant major depression (Yehuda et al. 1990, 1994, 1995). Second, it was reported that norepinephrine, a neurotransmitter frequently reported to be increased in PTSD, and the HPA axis might lead to the inhibition of cytokine secretion. Thus, since neopterin has been accepted as an important indicator of cellular immune system (Huber et al. 1984; Besedovsky et al. 1986), decreased neopterin levels in PTSD might be expected. The suppression of cellular immunity in PTSD has been supported by means of determining lower number of lymphocytes, T cells, and decreased natural killer cell activity (Inoue-Sakurai et al. 2000; Kawamura et al. 2001). Moreover, neopterin is the first intermediate in the synthesis of tetrahydrobiopterin, a cofactor for the hydroxylation of phenylalanine and tryptophan in a rate-limiting step in the biosynthesis of dopamine, noadrenaline and 5-hydroxytryptamine (5-HT) (Fuchs et al. 1988). These changes may be associated with PTSD symptoms becoming chronic and the poor response to trauma. In summary, there are close relations between PTSD and neopterin. However, it is controversial whether lower neopterin is a cause or result in PTSD.

Despite the fact that neopterin levels were reduced in patients with PTSD and that neopterin production was correlated with the severity of symptoms, it is clear that with sertraline treatment, an increase in neopterin levels was not evident. Furthermore, it did not appear that the change of CAPS scores over the 8 weeks of sertraline treatment was correlated with alterations of the neopterin levels. Consequently, it is tempting to speculate that the decreased neopterin production is a trait marker of PTSD.

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