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Study on serum cytokine levels in posttraumatic stress disorder patients

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ABSTRACT

Objective: To evaluate serum IL-2, IL-4, IL-6, IL-8, IL-10 and TNF-α levels in posttraumatic stress disorder (PTSD) patients. **Methods:** We utilized ELISA technology to examine cytokines such as IL-2, IL-4, IL-6, IL-8, IL-10 and TNF-α in serum from 50 well-characterized individuals with a primary DSM-Ⅳ PTSD diagnosis, and 50 age- and gender-matched healthy controls. We conservatively employed a Mann-Whitney U testing. **Results:** Individuals with primary PTSD had significantly elevated peripheral cytokine levels for all 6 different cytokines compared to age- and gender-matched healthy controls (all $P<0.01$). **Conclusions:** These findings suggest that a generalized inflammatory state may be present in individuals with PTSD.

1. Introduction

Posttraumatic stress disorder (PTSD) is an important manifestation of mental and behavioral disorders after disaster, including pathologically reexperiencing of traumatic events, avoidance to some clues related with trauma, continuous hyperarousal, and selective amnesia and emotional numbing to traumatic experience. Therefore, the patients feel miserable. PTSD is characterized by high morbidity, long duration and poor curative effect, seriously affecting medical treatment[1]. Although its etiopathogenesis is not entirely exact, the view that immune system is involved in PTSD attack is receiving increasing attention. The present study was aimed to detect and analyze the serum cytokines, like IL-2, IL-4, IL-6, IL-8, IL-10, TNF-α, *etc* in order to preliminarily explore the relationship between serum cytokine and PTSD.

2. Materials and methods

2.1. Study population

2.1.1. PTSD group

PTSD patients attending Psychological Counselling Center of People's Hospital of Hainan Province from January 2010 to December 2011 were included in the study. The inclusion criteria were scheduled according to Diagnostic and Statistical Manual of Mental Disorders, Fourth Edition (DSM-Ⅳ) and the diagnosis was made by psychiatric physician. The exclusion criteria were as follows: 1) patients with anxiety, panic and PTSD caused by various serious illnesses or in need of emergent intervention; 2) patients with gestation, substance use disorder, other mental disorders, long-term use of steriods and various types of diabetes mellitus.

2.1.2. Control group

Healthy individuals attending our hospital for normal check-up from January 2010 to December 2011 were included in the study and served as control. The inclusion criteria were as follows: 1) age and gender matched with PTSD group; 2) no serious illnesses associated with heart, liver, lungs, pancreas, kidney and other organs, no hematological diseases, no metabolic syndrome, gout, diabetes mellitus, hyperthyroidism, iron metabolic

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disturbance and other metabolic diseases after general physical examination and laboratory examination; 3) no history of mental disease; 4) no history of taking prescription drugs or OTC drugs. The research was approved by Medical Ethics Committee of our hospital and informed consent was obtained from each patient.
stored at −70 ℃ until they were analyzed.

2.2. Determination of serum IL-2, IL-4, IL-6, IL-8, IL-10 and TNF-α

All the patients were fasted in the morning and 4 mL of blood was taken from median cubital vein. All the sampling was completed in a week after the diagnosis was made for PTSD patients. Enzyme-linked immuno sorbent assay (ELISA) was used to determine the content of the above six cytokines. ELISA kits were purchased from Jianglai Biological Technology Co., Ltd., Shanghai.

2.3. Statistical analysis

All the values were expressed as mean±SD. All the data were entered into the computer and analyzed using SPSS statistical software of 11.5 version. Chi-square test was used for the comparison between the two groups. The mean data of the two groups were first subjected to normality test. If it obeyed the normal distribution, "t" test would be used, otherwise nonparametric test and Rank sum test were used. $P<0.05$ was considered to be significant and $P<0.01$ was considered to be highly significant.

3. Results

3.1. General information for study population

A total of 50 PTSD patients were included in the study, including 22 males and 28 females, aged 26-58 years old, with mean age of (42±12) years old, the duration lasted for 1-18 years which was averaged to be (9.48±6.25) years. The control group consisted of 50 cases, including 25 males and 25 females, aged 25-60 years old with mean age of (41±14) years old. The differences of the sex and age of the two groups were not statistically significant ($P>0.05$).

3.2. Comparison of the serum cytokine levels between PTSD group and control group

The unit for the content of serum cytokines was mol and the data did not obey the normal distribution. Normality test proved that nonparametric test and Mann-Whitney U test would be used for comparison between the two groups. Serum IL-2, IL-4, IL-6, IL-8, IL-10 and TNF-α levels were higher in PTSD group than that in control group. The differences between the two groups were statistically significant ($P<0.01$) (Table 1).

4. Discussion

Researches show that nervous-endocrine-immune systems are interrelated and interacted to regulate and maintain homeostasis in together. From the investigations, it was found that veterans coming back from Gulf War usually suffer from rheumatism, sarcoidosis, multiple sclerosis and other diseases associated with immune, revealing that immunological changes may be involved in the occurrence and maintainence of PTSD. Therefore, the proposed CK hypothesis of PTSD provides a new viewpoint to explore the etiology of PTSD and it is argued that PTSD is a disease pertaining to psychology, neurology and immune.

Maier and Watkins[2] deemed that brain and immune system constitue a two-way network in which immune system is a diffused sense organ of the brain and activation of immune cells can arouse a series of physiological, behavioral, emotional and cognitive changes. CK which is the sense organ of central nervous system (CNS) helps the brain recognize some non-cognitive stimulants such as virus, bacteria, antigens, cancer cell, *etc.* Therefore, CK and its receptors constitue the key mediators of CNS, neuroendocrine system and immune system. CK can affect human´s emotions and mental status. Although the mechanism is not clear, serum TNF-α, IL-6, sIL-1ra levels were elevated in healthy volunteers after intravenous injection with bacterial endotoxin, accompanied by anxiety, depression and cognitive disorder. IL-2 has an

Table 1
Comparison of the content of serum cytokines between PTSD group and control group.

Serum cytokines	PTSD group	Control group	*Z*
IL-2	12.18±3.86**	4.58±2.56	2.00
IL-4	115.20±35.2**	53.80±18.20	3.00
IL-6	16.28±5.68**	2.26±1.20	4.00
IL-8	49.25±24.26**	9.54±3.20	6.00
IL-10	6.45±4.26**	1.72±0.85	1.00
TNF-α	25.02±10.86**	5.36±1.28	5.00

**: $P<0.01$ when compared with control group.

obvious impact on cognition, for example, damage to the development of hippocampus and cognition is associated with deficiency of IL-2 gene. Treatment with IL-2 combined chemotherapy for some tumor patients will cause cognitive damage and PTSD symptoms will occur in hepatitis C patients receiving TNF-γ treatment[3].

Research findings reveal that in the status of depression, CK can activate hypothalamic-pituitary-adrenal (HPA) axis, eventually leading to the elevation of glucocorticoid; high levels of glucocorticoid can give a negative feedback act on hypothalamus and hypophysis of HPA axis, making the activation of HPA axis return to normal state. However, cytokines can inhibit the negative feedback, therefore leading to the excessive activation of HPA axis[4]. And in the status of PTSD, basic cortisone levels were reduced and the inhibition of HPA axis negative feedback was enhanced[5], revealing that CK may cross blood brain barrier to change the activation frequency of nervous cells and be involved in the regulation of different levels of dysfunction of HPA axis. Therefore, the bilateral reaction between immune system and HPA can maintain homeostasis, and integrity of the two systems is very important for the proper stress response.

At present, there are few immunological researches on PTSD and most of the researches are focused on chronic PTSD lasting for many years. It was found that obvious dysimmunity occurred in PTSD patients, the early study subjects whcih are mainly male war veterans, showing increased Th like cytokines in chronic PTSD, such as elevated plasma IL-6, IL-10, *etc*; the general skeleton map of cytokines in PTSD is similar to that in chronic stress mode, but lymphocyte subsets, the toxicity of natural killer cell Nk cell and delayed type hypersensitivity (DTH) are different[6-10]. To understand whether cytokines be involved in the pathogenesis of PTSD, the present study determined the levels of cytokines in 50 PTSD patients. The results showed that serum IL-2, IL-4, IL-6, IL-8, IL-10 and TNF-α levels were significantly higher in PTSD group than that in control group. IL-4, IL-6 and IL-10 are anti-inflammatory cytokines, revealing that PTSD is accompanied by activation of mononuclear phagocyte and lymphocyte. These cytokines play complicated roles in immune response, feedback increment of reduction of the content will occur. Particularly in acute stress and chronic stress, this feedback activity becomes more complicated because of different types and content of hormones. Therefore, an exact explanation for the elevated levels of the content of the above cytokines can not be given just from the clinical point, basci research should be carried out to know the exact mechanism. In addition, there is a need to perform further research to explore whether similar skeleton map of cytokines exists in acute PTSD or not, how the ratio of Th1/Th2 will change when Th1 like cytokines were taken into consideration, whether the changes exist in CNS, what roles do immune changes play in the etiology of PTSD.

Conflict of interest

The authors declare that they have no conflict of interest.

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