ANALYSIS ON CHANGES OF SERUM INFLAMMATORY CYTOKINES AND NEUROTRANSMITTERS IN PATIENTS WITH INSOMNIA COMBINED WITH DEPRESSION

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ABSTRACT

Introduction: *To investigate the changes of serum inflammatory cytokines interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-1β (IL-1β), soluble interleukin-2 receptor (sIL-2R), tumor necrosis factor-α (TNF-α) and neurotransmitters 5-hydroxytryptamine (5-HT), dopamine (DA) and norepinephrine (NE) in patients with insomnia combined with depression, and analyze their clinical significance.*

Materials and method: *One hundred and seventeen patients with insomnia combined with depression admitted to Shaoxing 7th people's hospital, China, from February 2020 to February 2022 were selected depressed group. Another 117 non-depressed patients with insomnia were selected as non-depressed group. According to the clinical efficacy after treatment, the depressed group was divided into effective and ineffective subgroups. Serum levels of IL-2, IL-6, IL-1β, sIL-2R, TNF-α, 5-HT, DA and NE were measured.*

Results: *Compared with non-depressed group, serum IL-2, IL-6, IL-1β, sIL-2R and TNF-α levels in depressed group before treatment were higher (all P<0.001); but serum 5-HT, NE and DA levels were the opposite (all P<0.001). Compared with the depressed group before treatment, above serum inflammatory cytokines levels in the depressed group after treatment were lower (all P<0.001), but above serum neurotransmitters levels were the opposite (all P<0.001). Above serum inflammatory cytokines levels in effective subgroup after treatment were lower than in ineffective subgroup (P=0.003, P=0.001, P<0.001, P<0.001 and P<0.001, respectively). Above serum neurotransmitters levels in effective subgroup after treatment were higher than in ineffective subgroup (P=0.004, P=0.037 and P<0.001, respectively).*

Conclusion: *Above serum inflammatory cytokines and neurotransmitters are closely related to the condition of patients with insomnia combined with depression. After treatment the above serum inflammatory cytokine levels are reduced to some extent, while the above neurotransmitter levels are increased to some extent. The above-mentioned inflammatory cytokines and neurotransmitters may be valuable in the diagnosis of insomnia combined with depression and the evaluation of treatment effects.*

Keywords: *Insomnia, depression, inflammatory, cytokines, neurotransmitters.*

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Introduction

Insomnia is a group of conditions characterized by frequent failure to obtain a normal duration and quality of sleep[(1)]. Patients with insomnia are prone to combine depression and other mental conditions. Insomnia is not only a symptom of depression, but also an important factor in causing depression[(2)]. There may be a correlation between insomnia and depression[(3)]. The abnormal secretion of inflammatory cytokines affects the function of neural networks in the brain and causes mood changes. Cytokines are one of the important regulators in the inflammatory mechanisms of depression[(4)]. Interleukin-2 (IL-2), interleukin-6 (IL-6), interleukin-1β (IL-1β), soluble interleukin-2 receptor (sIL-2R) and tumor necrosis factor-α (TNF-α) are important inflammatory cytokines. IL-2, IL-6, IL-1β, SIL-2R and TNF-α are all capable of promoting the secretion of multiple inflammatory mediators involved in the regulation

of depression pathogenesis[5, 6]. Depression is also associated with neurotransmitters[7]. The parasecretion of neurotransmitters including 5-hydroxytryptamine (5-HT), dopamine (DA) and norepinephrine (NE) can trigger depressive disorders[8, 9]. Neurotransmitters above are also associated with insomnia[10, 11]. Currently, there are few studies on changes of the above serum inflammatory cytokines and neurotransmitters in patients with insomnia combined with depression before and after treatment.

The aim of the present study was to investigate the changes of serum inflammatory cytokines and neurotransmitters in patients with insomnia combined with depression before and after treatment, and analyze their clinical significance.

Materials and methods

Clinical materials

One hundred and seventeen patients with insomnia combined with depression admitted to Shaoxing 7th people's hospital, China, from February 2020 to February 2022 were selected depressed group.

The inclusion criteria were:

• Patients who met the diagnostic criteria of insomnia, with Pittsburgh Sleep Quality Index questionnaire (PSQI) score >7, and also met the diagnostic criteria of depression, with Hamilton depression scale (HAMD) score ≥8;

• Age ≥18 years old, but <65 years old;

• If patients combined with anxiety, depression should be a main symptom, namely Hamilton anxiety scale (HAMA) score lower than HAMD score;

• Patients who gave informed consent to this study.

The exclusion criteria were:

• Patients who had used drugs for depression and insomnia within 1 month prior to enrollment;

• Patients with severe physical illness;

• Patients with allergies to the study drugs;

• Patients with severe suicidal tendencies;

• Lactating and pregnant women;

• Patients combined with severe psychiatric disorders;

• Secondary insomnia;

• Those with poor treatment compliance;

• Those with hearing and reading impairment or inability to communicate with physicians.

Another 117 non-depressed patients with insomnia (PSQI score >7 and HAMD score <8) who were matched with the age and gender of the depressed group were selected as the non-depressed group during the same period.

Methods

Patients in the depressed group were treated with paroxetine hydrochloride tablets combined with zolpidem tartrate tablets for 8 weeks. Paroxetine hydrochloride tablets were administered orally once a day at 10 mg/dose, and gradually increased to 20 mg/dose after 7 d of administration. Zolpidem tartrate tablets were taken orally every night half an hour before bedtime at 10mg/dose.

After 8 weeks of treatment, the clinical efficacy of the depressed group was assessed by the reduction rate of HAMD score and PSQI score.The reduction rate of HAMD scale score = [(pre-treatment score - post-treatment score)/pre-treatment score] × 100%. The reduction rate of PSQI scale score = [(pre-treatment score - post-treatment score)/pre-treatment score] × 100%. After treatment, both HAMD score and PSQI score reduction rate≥75% was considered as cured; both HAMD score and PSQI score reduction rate ≥50% but < 75% was considered as apparently effective; both HAMD score and PSQI score reduction rate ≥25% was considered as effective; and both HAMD score and PSQI score reduction rate <25% was considered as ineffective. According to the clinical efficacy after treatment, the depressed group was divided into effective and ineffective subgroups. Patients with cured, apparently effective and effective results in the depressed group after treatment were included in the effective subgroup, while patients with ineffective results after treatment in the depressed group were included in the ineffective subgroup.

The serum levels of inflammatory cytokines IL-2, IL-6, IL-1β, sIL-2R, TNF-α and neurotransmitters 5-HT, NE, DA were measured by enzyme-linked immunosorbent assay before and after 8 weeks of treatment in the depressed group, and at time of hospital admission in the non-depressed group, respectively.

Statistic analysis

SPSS 25.0 software was used for data analysis. Measurement data were expressed by mean±standard deviation. Measurement data of depressed group before and after treatment were compared by paired t-test. Independent sample t-test was used to compare the measurement data between the depressed group and non-depressed group. $P<0.05$ was considered statistically significant.

Results

There were 53 (45.30%) males and 64 (54.70%) females in the depressed group, aged 35-62 (49.76±5.79) years old. There were 54 (46.15%) males and 63 (53.85%) females in the non-depressed group, aged 35-61(49.56±5.06) years old.

The serum levels of inflammatory cytokines IL-2, IL-6, IL-1β, sIL-2R and TNF-α in the depressed group before treatment were higher than in the non-depressed group (all P<0.001), as shown in Table 1. The serum levels of neurotransmitters 5-HT, NE and DA in the depressed group before treatment were lower than in the non-depressed group (all P<0.001), as shown in Table 1.

Parameter	Depressed group before treatment (n=117)	Non-depressed group (n=117)	P value
Serum IL-2 (pg/mL)	46.02±3.55	30.57±2.36	<0.001
Serum IL-6 (ng /L)	24.39±1.89	21.53±1.66	<0.001
Serum IL-1β (pg/mL)	24.67±1.93	15.85±1.20	<0.001
Serum sIL-2R (pmol/mL)	69.82±5.47	41.01±3.12	<0.001
Serum TNF-α (pg/mL)	28.47±2.23	16.85±1.28	<0.001
Serum 5-HT (pg/mL)	24.58±1.94	47.25±3.59	<0.001
Serum NE (μg/mL)	5.30±0.46	11.33±0.91	<0.001
Serum DA (pg/mL)	46.95±4.05	77.41±6.42	<0.001

Table 1: Comparison of serum inflammatory cytokines and neurotransmitters between the depressed group before treatment and non-depressed group.

The serum levels of inflammatory cytokines IL-2, IL-6, IL-1β, sIL-2R and TNF-α in the depressed group after treatment were lower than in the depressed group before treatment (all P<0.001), as shown in Table 2. The serum levels of neurotransmitters 5-HT, NE and DA in the depressed group after treatment were higher than in the depressed group before treatment (all P<0.001), as shown in Table 2.

Parameter	Depressed group before treatment (n=117)	Non-depressed group (n=117)	P value
Serum IL-2 (pg/mL)	46.02±3.55	34.63±2.81	<0.001
Serum IL-6 (ng /L)	24.39±1.89	22.06±1.79	<0.001
Serum IL-1β (pg/mL)	24.67±1.93	19.32±1.57	<0.001
Serum sIL-2R (pmol/mL)	69.82±5.47	50.76±4.12	<0.001
Serum TNF-α (pg/mL)	28.47±2.23	21.22±1.77	<0.001
Serum 5-HT (pg/mL)	24.58±1.94	42.81±3.59	<0.001
Serum NE (μg/mL)	5.30±0.46	9.95±0.83	<0.001
Serum DA (pg/mL)	46.95±4.05	71.83±6.02	<0.001

Table 2: Comparison of serum inflammatory cytokines and neurotransmitters before and after treatment in the depressed group.

After 8 weeks of treatment, 31 (26.50%) patients in the depressed group were cured, 33 (28.21%) were apparently effective, 30 (25.64%) were effective, and 23 (19.66%) were ineffective. Therefore, the patients with cured, apparently effective and effective results in the depressed group after treatment were included in the effective subgroup (n=94), and 23 patients with ineffective results in the depressed group after treatment were included in the ineffective subgroup (n=23). The serum levels of inflammatory cytokines IL-2, IL-6, IL-1β, sIL-2R and TNF-α in the effective subgroup after treatment were lower than in the ineffective subgroup (P=0.003, P=0.001, P<0.001, P<0.001 and P<0.001, respectively), as shown in Table 3.

The serum levels of neurotransmitters 5-HT, NE and DA in the effective subgroup after treatment were higher than in the ineffective subgroup (P=0.004, P=0.037 and P<0.001, respectively), as shown in Table 3.

Parameter	Effective subgroup (n=94)	Ineffective subgroup (n=23)	P value
Serum IL-2 (pg/mL)	34.26±2.84	36.18±2.10	0.003
Serum IL-6 (ng /L)	21.79±1.81	23.16±1.20	0.001
Serum IL-1β (pg/mL)	18.99±1.48	20.64±1.17	<0.001
Serum sIL-2R (pmol/mL)	49.96±4.00	54.12±2.66	<0.001
Serum TNF-α (pg/mL)	20.81±1.60	22.90±1.33	<0.001
Serum 5-HT (pg/mL)	43.28±3.60	40.89±2.92	0.004
Serum NE (μg/mL)	10.03±0.86	9.63±0.62	0.037
Serum DA (pg/mL)	73.25±5.59	66.01±3.87	<0.001

Table 3: Comparison of serum inflammatory cytokines and neurotransmitters between the effective and ineffective subgroups after treatment.

Discussion

The coexistence of insomnia and depression may have an intrinsic neural correlation mechanism. It is possible that inflammatory cytokines are the pathophysiological basis for the association of insomnia and depression[12]. The secretion of inflammatory cytokines may be a cause of depressive disorders[13]. Studies have found that inflammatory cytokines such as IL-2, IL-6, IL-1β, sIL-2R and TNF-α are thought to activate the hypothalamic-pituitary-adrenal axis to cause depressed mood[14, 15].

This study found that the levels of serum inflammatory cytokines IL-2, IL-6, IL-1β, sIL-2R and TNF-α in the depressed group before treatment were higher than in the non-depressed group, indicating that serum inflammatory cytokines in the

depressed group are higher than in the non-depressed group. The findings of this study are generally consistent with the meta-analysis of Liu et al., who concluded that depressed patients had elevated levels of sIL-2R, TNF-α and IL-6[16]. Studies have found that serum IL-6 and TNF-α levels in patients with insomnia combined with depression do not differ from those in the healthy population[17]. However, some studies have shown that depressed patients have significantly higher levels of inflammatory factors such as IL-1β and TNF-α compared to the healthy population[18].

The inconsistent results reported in the previous studies mentioned above may presumably be influenced by factors such as sample size, race, age, and inflammatory cytokine levels subject to genetic polymorphisms. Due to the limitations of the study, the serum levels of inflammatory cytokines such as IL-6 and TNF-α in patients with insomnia combined with depression were not compared with the healthy population in this study, which needs further investigation. Furthermore, this study also found that the levels of the above inflammatory cytokines in the depressed group after treatment were lower than in the depressed group before treatment. This may be due to the regulation of the immune status in the depressed group after treatment, followed by the downregulation of serum inflammatory cytokine levels in patients[15].

Monoamine neurotransmitters such as 5-HT, NE and DA are closely related to mood regulation and psychological stress responses[19]. 5-HT, NE and DA are excitatory neurotransmitters, and patients with low levels of them show insufficient excitability and are prone to be in depressed mood. 5-HT, NE and DA are involved in regulating human emotional and affective activities, and their abnormal functions play a key role in the development of mental-emotional related disorders. In this study, serum 5-HT, NE, and DA levels in patients with insomnia combined with depression were found to be lower than in non-depressed patients with insomnia. This enriches the understanding of the pathogenesis of patients with insomnia combined with depression.

The treatment of patients with depression requires increasing the function of the monoamine neurotransmitters 5-HT, NE and DA in the central nervous system and increasing the concentration levels of 5-HT, NE and DA in the synaptic gap. The serum levels of neurotransmitters 5-HT, NE and DA in the depressed group after treatment were higher than in the depressed group before treatment. Patients in the depressed group after treatment were divided into two subgroups for analysis, namely effective and ineffective subgroups, and serum neurotransmitter 5-HT, NE and DA levels in the effective subgroup were found to be higher than in the ineffective subgroup. It suggests that there is a relationship between elevated levels of neurotransmitters 5-HT, NE and DA and the treatment efficacy of patients with insomnia combined with depression. The reason may be that the levels of inflammatory cytokines such as IL-2, IL-6, IL-1β, SIL-2R and TNF-α were downregulated in patients with insomnia combined with depression after treatment, which in turn affected the metabolic activity of central neurotransmitters in patients and promoted the increase in the levels of neurotransmitters 5-HT, NE and DA[20].

The number of patients included in the research was limited, especially the number of patients in the ineffective subgroup of the depressed group was small, which may cause some errors in the research results and need further validation of the results of this study in subsequent large sample studies.

Conclusion

Serum inflammatory cytokines IL-2, IL-6, IL-1β, sIL-2R, TNF-α and neurotransmitters 5-HT, NE, DA are closely related to the condition of patients with insomnia combined with depression. After treatment the above serum inflammatory cytokine levels are reduced to some extent, while the above neurotransmitter levels are increased to some extent. The above-mentioned inflammatory cytokines and neurotransmitters may be valuable in the diagnosis of insomnia combined with depression and the evaluation of treatment effects.

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