



# Effect of anxiety and depression on serum neurotransmitters and immune function in patients with cervical cancer chemotherapy

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## ABSTRACT

**Objective:** To study the effect of anxiety and depression on serum neurotransmitters and immune function in patients with cervical cancer chemotherapy. **Methods:** Patients with advanced cervical cancer who received chemotherapy in the First Affiliated Hospital of Chengdu Medical College between May 2014 and June 2016 were selected, HAMA scores and HAMD scores were used to assess anxiety and depression and divide the patients into control group, depression group, anxiety group and depression + anxiety group. The contents of monoamine neurotransmitters and immune cytokines in serum as well as the expression of immune transcription factors in peripheral blood mononuclear cells were detected. **Results:** Serum NE, E, 5-HT, 5-HIAA and DOPAC contents of depression group and depression + anxiety group were significantly lower than those of control group, and serum NE, E, 5-HT, 5-HIAA and DOPAC contents of anxiety group were significantly higher than those of control group; peripheral blood T-bet mRNA expression as well as serum IFN- $\gamma$  and TNF- $\alpha$  contents of depression group, anxiety group and depression + anxiety group were significantly lower than those of control group while GATA3, Foxp3 and ROR $\gamma$ t mRNA expression as well as serum IL-4, TGF- $\beta$  and IL-17 contents were significantly higher than those of control group; peripheral blood T-bet mRNA expression as well as serum IFN- $\gamma$  and TNF- $\alpha$  contents of depression + anxiety group were significantly lower than those of depression group and anxiety group while GATA3, Foxp3 and ROR $\gamma$ t mRNA expression as well as serum IL-4, TGF- $\beta$  and IL-17 contents were significantly higher than those of depression group and anxiety group. **Conclusion:** Anxiety and depression in patients with cervical cancer chemotherapy can affect the secretion of monoamine neurotransmitters, the differentiation of CD4+T cell subsets and the antitumor immune response mediated by them.

## 1. Introduction

Cervical cancer is a common malignant tumor of female reproductive system, early cervical cancer is mainly by surgery treatment, and advanced cervical cancer requires radiotherapy and chemotherapy to prolong survival time[1,2]. Although chemotherapy drugs can effectively kill tumor cells, they can also lead to normal cell damage and cause negative emotions such as anxiety and depression. The anxiety, depression and other negative emotions

in patients with cervical cancer chemotherapy will not only affect patients' daily life and treatment compliance, but can also aggravate the damaged homeostasis and unbalanced immune response caused by the side effects of chemotherapy drugs[3,4]. In spite of this, the occurrence mechanism of negative emotions such as anxiety and depression in patients with cervical cancer chemotherapy is still not clear, and there is no related report about the change of immune function. "Monoamine neurotransmitter hypothesis" is a possible occurrence mechanism of depression and anxiety, and the abnormal secretion of monoamine neurotransmitters is associated with the occurrence of anxiety and depression. In the following studies, the effect of anxiety and depression on serum neurotransmitters and immune function in patients with cervical cancer chemotherapy was analyzed.

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## 2. Case information and research methods

### 2.1 Inclusion and exclusion criteria

The inclusion criteria were as follows: (1) the patients who were diagnosed with advanced cervical cancer in the First Affiliated Hospital of Chengdu Medical College between May 2014 and June 2016; (2) those who received the TP regimen (taxol + cisplatin) or TC regimen (taxol + carboplatin) chemotherapy; (3) those with the expected survival time > 6 months; (4) those who signed informed consent. The exclusion criteria were as follows: (1) patients who were associated with autoimmune diseases; (2) the patients who used immune agent; (3) patients associated with mental illness.

### 2.2 Case information

A total of 116 patients were enrolled, the HAMA scores and the HAMD scores were used to assess the anxiety and depression and then divide the patients into the control group, depression group, anxiety group and depression + anxiety group. The control group ( $n=47$ ) were with HAMA scores  $\leq 14$  points and HAMD scores  $\leq 24$  points; the depression group ( $n=28$ ) were with HAMA scores 14 points and HAMD scores > 24 points; the anxiety group ( $n=23$ ) were with HAMA scores > 14 points and HAMD scores  $\leq 24$  points; the depression + anxiety group ( $n=18$ ) were with HAMA scores > 14 points and HAMD scores > 24 points.

### 2.3 Serum monoamine neurotransmitter and immune cytokine detection methods

On the same day of HAMA scoring and HAMD scoring, 5 mL peripheral venous blood was collected, let stand at room temperature and then centrifuged to separate the upper serum, and enzyme-linked immunosorbent assay kits were used to detect the levels of NE, E, 5-HT, 5-HIAA, DOPAC, IFN- $\gamma$ , TNF- $\alpha$ , IL-4, TGF- $\beta$  and IL-17.

### 2.4 Peripheral blood immune cell transcription factor expression detection methods

On the same day of HAMA scoring and HAMD scoring, 1-2 mL peripheral venous blood was collected, anti-coagulated with heparin

sodium, added in lymphocyte separation medium and centrifuged to separate the mononuclear cells in the middle tier, the cells were washed with PBS and centrifuged twice to extraction RNA, it was synthesized into cDNA after reverse transcription for fluorescence quantitative PCR reaction, and T-bet, GATA3, Foxp3 and ROR  $\gamma$  t mRNA expression were determined.

### 2.5 Statistical methods

SPSS 20.0 software was used to input and analyze data, measurement data comparison among four groups was by variance analysis and  $P < 0.05$  indicated statistical significance in differences.

## 3. Results

### 3.1 Serum monoamine neurotransmitter contents

Analysis of serum monoamine neurotransmitters NE, E, 5-HT, 5-HIAA and DOPAC contents among four groups of patients was as follows: serum NE, E, 5-HT, 5-HIAA and DOPAC contents of depression group and depression + anxiety group were significantly lower than those of control group; serum NE, E, 5-HT, 5-HIAA and DOPAC contents of anxiety group were significantly higher than those of control group; serum NE, E, 5-HT, 5-HIAA and DOPAC contents of depression + anxiety group were significantly higher than those of depression group.

### 3.2 Peripheral blood immune cell transcription factor expression

Analysis of peripheral blood immune cell transcription factors T-bet, GATA3, Foxp3 and ROR  $\gamma$  t expression among four groups of patients was as follows: peripheral blood T-bet mRNA expression of depression group, anxiety group and depression + anxiety group were significantly lower than that of control group while GATA3, Foxp3 and ROR  $\gamma$  t mRNA expression were significantly higher than those of control group; peripheral blood T-bet mRNA expression of depression + anxiety group was significantly lower than that of depression group and anxiety group while GATA3, Foxp3 and ROR  $\gamma$  t mRNA expression were significantly higher than those of depression group and anxiety group.

**Table 1.**

Comparison of serum monoamine neurotransmitters among four groups of patients.

Groups	n	NE	E	5-HT	5-HIAA	DOPAC
Control group	47	3.92±0.52	3.74±0.49	113.42±16.93	0.34±0.05	128.49±14.58
Depression group	28	2.21±0.35 <sup>a</sup>	1.87±0.25 <sup>a</sup>	89.32±11.25 <sup>a</sup>	0.20±0.03 <sup>a</sup>	92.31±11.27 <sup>a</sup>
Anxiety group	23	4.88±0.74 <sup>b</sup>	4.65±0.56 <sup>b</sup>	137.45±16.72 <sup>b</sup>	0.47±0.08 <sup>b</sup>	140.28±17.68 <sup>b</sup>
Depression + anxiety group	18	3.14±0.46 <sup>ab</sup>	2.52±0.38 <sup>ab</sup>	98.31±10.38 <sup>ab</sup>	0.27±0.04 <sup>ab</sup>	110.32±16.27 <sup>ab</sup>

<sup>a</sup>: compared with control group,  $P < 0.05$ ; <sup>b</sup>: compared with anxiety group,  $P < 0.05$ ; <sup>ab</sup>: compared with depression group,  $P < 0.05$ .

**Table 2.**

Comparison of peripheral blood immune cell transcription factor expression among four groups of patients.

Groups	n	T-bet	GATA3	Foxp3	ROR $\gamma$ t
Control group	47	2.78±0.44	0.45±0.07	0.42±0.04	0.39±0.05
Depression group	28	1.52±0.18 <sup>a</sup>	0.77±0.09 <sup>a</sup>	0.73±0.10 <sup>a</sup>	0.80±0.12 <sup>a</sup>
Anxiety group	23	1.63±0.20 <sup>a</sup>	0.81±0.10 <sup>a</sup>	0.76±0.09 <sup>a</sup>	0.74±0.08 <sup>a</sup>
Depression + anxiety group	18	1.02±0.16 <sup>ab</sup>	1.04±0.18 <sup>ab</sup>	1.05±0.14 <sup>ab</sup>	1.01±0.13 <sup>ab</sup>

<sup>a</sup>: compared with control group,  $P < 0.05$ ; <sup>b</sup>: compared with anxiety group,  $P < 0.05$ ; <sup>ab</sup>: compared with depression group,  $P < 0.05$ .

**Table 3.**

Comparison of serum immune cytokines among four groups of patients.

Groups	n	IFN- $\gamma$	TNF- $\alpha$	IL-4	TGF- $\beta$	IL-17
Control group	47	24.59±4.51	11.38±1.62	37.83±6.41	33.49±5.21	25.51±3.51
Depression group	28	16.62±2.58 <sup>*</sup>	7.97±0.94 <sup>*</sup>	50.28±7.78 <sup>*</sup>	47.52±6.72 <sup>*</sup>	39.38±6.27 <sup>*</sup>
Anxiety group	23	17.03±1.98 <sup>*</sup>	8.02±1.15 <sup>*</sup>	51.12±7.62 <sup>*</sup>	48.11±6.94 <sup>*</sup>	38.11±5.89 <sup>*</sup>
Depression + anxiety group	18	11.25±1.63 <sup>ab</sup>	5.26±0.78 <sup>ab</sup>	78.94±9.35 <sup>ab</sup>	59.35±8.25 <sup>ab</sup>	52.37±7.28 <sup>ab</sup>

<sup>\*</sup>: compared with control group,  $P < 0.05$ ; <sup>a</sup>: compared with depression group,  $P < 0.05$ ; <sup>b</sup>: compared with anxiety group,  $P < 0.05$ .

### 3.3 Serum immune cytokine contents

Analysis of serum immune cytokines IFN-  $\gamma$  (ng/L), TNF-  $\alpha$  ( $\mu$ g/L), IL-4 (ng/L), TGF-  $\beta$  ( $\mu$ g/L) and IL-17 (ng/L) contents among four groups of patients was as follows: serum IFN-  $\gamma$  and TNF-  $\alpha$  contents of depression group, anxiety group and depression + anxiety group were significantly lower than those of control group while IL-4, TGF-  $\beta$  and IL-17 contents were significantly higher than those of control group; serum IFN-  $\gamma$  and TNF-  $\alpha$  contents of depression + anxiety group were significantly lower than those of depression group and anxiety group while IL-4, TGF-  $\beta$  and IL-17 contents were significantly higher than those of depression group and anxiety group.

## 4. Discussion

In recent years, the anxiety, depression and other negative emotions produced in the process of malignant tumor chemotherapy have received more and more attention, but the mechanism of the negative emotions such as anxiety and depression during cervical cancer chemotherapy is still not clear, and there is no related report about the effect of negative emotions on the immune function. "Monoamine neurotransmitter hypothesis" is the highly recognized pathogenesis of depression and anxiety, and the occurrence of anxiety and depression is closely related to the abnormal secretion of NE, E, 5-HT, DA and other monoamine neurotransmitters[5]. NE and E are released by the peripheral sympathetic postganglionic neurons and adrenergic nerve endings in the brain, and can maintain the excitability of the nerves[6,7]. 5-HT comes from the 5-serotonergic neuron in the brain and causes mood changes by acting on receptors, and 5-HIAA is its inactive metabolite[8]; DA comes from the dopaminergic neuron in the brain, it acts on the prefrontal cortex and causes anxiety, and the DOPAC is its inactive metabolite[9]. To define the relationship of monoamine neurotransmitter changes with the occurrence of anxiety and depression during cervical cancer chemotherapy, the serum contents of above monoamine neurotransmitters in four groups of patients were analyzed in the study, and the results showed that serum NE, E, 5-HT, 5-HIAA and DOPAC contents of depression group and depression + anxiety group were significantly lower than those of control group; serum

NE, E, 5-HT, 5-HIAA and DOPAC contents of anxiety group were significantly higher than those of control group. This means that the occurrence of anxiety during cervical cancer chemotherapy is related to the excessive secretion of monoamine neurotransmitters, and the occurrence of depression is associated with the insufficient secretion of monoamine neurotransmitters; the combination of anxiety and depression can also lead to changes in monoamine neurotransmitters, and depression is the major change, which is characterized by the decrease in corresponding neurotransmitters.

When cervical cancer patients undergo chemotherapy, the anxiety and depression caused by monoamine neurotransmitter changes would further cause the destruction of the homeostasis and the disorder of immune response. The chemotherapy drugs have certain side effects of their own, they can cause immune cell damage and inhibit the immune response, and the combination of anxiety and depression will further aggravate the inhibition of the immune response. CD4+T lymphocytes are the important cells that exert anti-tumor immune response in the occurrence and development of malignant tumor, and under the action of different transcription factors, they differentiate into different subsets and mediate the corresponding immune response[10]. T-bet and GATA-3 are the transcription factors that regulate CD4+T lymphocyte subgroups Th1 and Th2 differentiation respectively, the former has anticancer effect after differentiation and maturation, and the latter will inhibit the antitumor immune response after differentiation and maturation[11]; Foxp3 and ROR  $\gamma$  t are the transcription factors that adjust Treg and Th17 differentiation respectively, the former has negative immunomodulatory effect after differentiation and maturation, and the latter can promote the cancer cell growth and infiltration after differentiation and maturation[12]. In the study, the analysis of above transcription factor expression in peripheral blood showed that peripheral blood T-bet mRNA expression of depression group, anxiety group and depression + anxiety group were significantly lower than that of control group while GATA3, Foxp3 and ROR  $\gamma$  t mRNA expression were significantly higher than those of control group, and the changes in above transcription factor expression in peripheral blood of depression + anxiety group were more significant than those of depression group and anxiety group. This suggests that the anxiety and depression in patients with cervical cancer chemotherapy will affect the differentiation of the CD4+T cell subsets.

After differentiation and maturation, the Th1, Th2, Treg, Th17

and other CD4+T cell subsets are able to participate in the immune response process by secreting the corresponding cytokines. The IFN- $\gamma$  and TNF- $\alpha$  secreted by Th1 play the roles of positively regulating cellular immune response and killing cancer cells, and IFN- $\gamma$  can also promote NK cell differentiation and maturation, and increase the tumor-killing effect of NK cells[13,14]; the IL-4, IL-5 and IL-10 secreted by Th2 have negative regulatory effect and can facilitate the immune escape of cancer cells[15]; Treg cells can exert negative immunomodulatory effect through intercellular contact, and can also secrete TGF- $\beta$  1 to suppress the differentiation and maturation of a variety of lymphocytes[16]; the IL-17 secreted by Th17 has a certain promoting effect on the proliferation, migration, invasion and other malignant biological behaviors of cancer cells[17]. In order to further clarify the effect of anxiety and depression on CD4+T cell subset differentiation in patients with cervical cancer chemotherapy, the contents of these cytokines in serum were analyzed in the study, and the results showed that serum IFN- $\gamma$  and TNF- contents of depression group, anxiety group and depression + anxiety group were significantly lower than those of control group while IL-4, TGF- $\beta$  and IL-17 contents were significantly higher than those of control group, and the changes in above cytokine contents in serum of depression + anxiety group were more significant than those of depression group and anxiety group. This further confirms that anxiety and depression in patients with cervical cancer chemotherapy can inhibit the differentiation of the CD4+T cell subset Th1 and promote the differentiation of Th2, Treg and Th17.

To sum up, it is believed that the anxiety and depression during cervical cancer chemotherapy can affect monoamine neurotransmitter secretion, anxiety increases neurotransmitter secretion, and depression decreases neurotransmitter secretion; at the same time, the anxiety and depression will also impact the differentiation of the CD4+T cell subsets Th1, Th2, Treg and Th17 as well as the anti-tumor immune response mediated by them.

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