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Changes of serum endocrine hormone levels in patients with cancer-related fatigue and their correlation with anti-tumor immune response and tumor load

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ABSTRACT

Objective: To study the changes of serum endocrine hormone levels in patients with cancer-related fatigue (CRF) and their correlation with anti-tumor immune response and tumor load. **Methods:** A total of 137 patients who were diagnosed with primary lung cancer in West China Hospital, Sichuan University between June 2014 and November 2016 were selected and then divided into CRF group and control group according to their self-reported symptoms, serum was collected to determine the levels of endocrine hormones and tumor markers, and peripheral blood was collected to detect the levels of immune cells. **Results:** Serum ACTH and TSH levels of CRF group were significantly higher than those of control group while Cor, FT3 and FT4 levels were significantly lower than those of control group; peripheral blood $CD11b^{+}CD15^{-}CD33^{+}CD14^{+}$M-MDSC, $CD11b^{+}CD15$-$CD33^{+}CD14^{-}$G-MDSC, $CD4^{+}CD25^{+}CD127^{low}$Treg and $CD19^{+}CD5^{+}CD1d^{+}$Breg levels as well as serum CEA, Cyfra21-1, SCC-Ag, HE4, GDF-15 and PCNA levels of CRF group were significantly higher than those of control group, positively correlated with serum ACTH and TSH levels, and negatively correlated with Cor, FT3 and FT4 levels. **Conclusion:** The changes of thyroid hormone and adrenal cortical hormone levels in patients with cancer-related fatigue are closely related to the inhibited anti-tumor immune response and increased tumor load.

1. Introduction

Cancer-related fatigue (CRF) is a common simultaneous phenomenon in patients with malignant tumor, the hypermetabolism caused by the cancer itself and the psychological mood change can cause fatigue, and the adverse reactions during radiotherapy and chemotherapy can also cause fatigue[1,2]. The emergence of CRF will affect the daily life as well as the compliance to the treatment of patients with malignant tumor, it will also result in antitumor immune response disorder and tumor load increase, but the specific mechanism of CRF is not yet clear. The hypothalamus-pituitary-thyroid axis and the hypothalamus-pituitary-adrenal cortex axis are the important endocrine target gland axis, persistent fatigue status can affect the function of endocrine glands and cause the changes in levels of corresponding endocrine hormones, and the endocrine hormone disorder will affect material and energy metabolism to increase the fatigue state[3]. In the study, we specifically analyzed the changes of serum endocrine hormone levels in patients with cancer-related fatigue and their correlation with anti-tumor immune response and tumor load.

2. Case information and research methods

2.1 General case information

A total of 137 patients who were diagnosed with primary lung cancer in West China Hospital, Sichuan University between June 2014 and November 2016 were selected, and all patients were diagnosed with lung cancer by pathological examination, had finished comprehensive lung cancer treatment (used two or more

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than two anti-cancer drugs), were with Kamofsky Performance Status 80 points, and were without history of endocrine disease, anemia and other blood diseases. After admission, patients were divided into CRF group and control group according to their self-reported symptoms. There were 55 patients in CRF group, including 33 men and 22 women that were 58-73 years old and with Kamofsky Performance Status (85.2±9.5) points; there were 82 cases in control group, including 52 men and 39 women that were 56-72 years old and with Kamofsky Performance Status (85.8±8.8) points. There was no statistically significant difference in general information between the two groups (P>0.05).

2.2 Serum index detection

3 mL peripheral venous blood was collected after admission, let stand at room temperature for 15 minutes and then centrifuged for 10 min at 3 000 r/min to get upper serum, electrochemical luminescence kit was used to determine ACTH, Cor, TSH, FT3 and FT4 contents, and enzyme-linked immunosorbent assay kit was used to determine the content of CEA, Cyfra21-1, SCC-Ag, HE4, GDF-15 and PCNA.

2.3 Peripheral blood immune cell detection

3 mL peripheral venous blood was collected after admission, fluorescent antibody of CD4, CD5, CD11, CD14, CD15, CD19, CD25, CD33 and CD127 were incubated, joined by Permeabilisation and continuously incubated, and then flow cytometer was used to determine the levels of $CD11b^+CD15\text{-}CD33^+CD14^+$M-MDSC, $CD11b^+CD15\text{-}CD33^+CD14$-G-MDSC, $CD4^+CD25^+CD127^{low}$Treg and $CD19^+CD5^+CD1d^+$Breg.

2.4 Statistical methods

SPSS 19.0 software was used to input data, differences in data between two groups were analyzed by test and P<0.05 indicated statistical significance in differences in test results.

3. Results

3.1 Serum endocrine hormone levels

Analysis of serum endocrine hormones ACTH, Cor (nmol/L), TSH (mU/L), FT3 (pmol/L) and FT4 (pmol/L) levels between two groups of patients was as follows: serum ACTH and TSH levels of CRF group were significantly higher than those of control group while Cor, FT3 and FT4 levels were significantly lower than those of control group. Differences in serum ACTH, Cor, TSH, FT3 and FT4 levels were statistically significant between two groups of patients (P<0.05).

3.2 Peripheral blood immune cell levels

Analysis of peripheral blood immune cells $CD11b^+CD15^-CD33^+CD14^+$M-MDSC, $CD11b^+CD15^-CD33^+CD14^-$G-MDSC, $CD4^+CD25^+CD127^{low}$Treg and $CD19^+CD5^+CD1d^+$Breg levels between two groups of patients was as follows: peripheral blood M-MDSC, G-MDSC, Treg and Breg levels of CRF group were significantly higher than those of control group. Differences in peripheral blood M-MDSC, G-MDSC, Treg and Breg levels were statistically significant between two groups of patients (P<0.05). Pearson correlation analysis showed that peripheral blood M-MDSC, G-MDSC, Treg and Breg levels in CRF group were positively correlated with serum ACTH and TSH levels, and negatively correlated with serum Cor, FT3 and FT4 levels.

3.3 Serum tumor marker levels

Analysis of serum tumor markers CEA (ng/mL), Cyfra21-1 (ng/mL), SCC-Ag (ng/mL), HE4 (pg/mL), GDF-15 (ng/mL) and PCNA (ng/mL) levels between two groups of patients was as follows: serum CEA, Cyfra21-1, SCC-Ag, HE4, GDF-15 and PCNA levels of CRF group were significantly higher than those of control group.

Table 1.
Comparison of serum endocrine hormones between two groups of patients.

Groups	n	ACTH	Cor	TSH	FT3	FT4
CRF group	55	98.34±11.28	103.52±15.63	3.28±0.56	3.49±0.52	13.41±1.87
Control group	82	57.64±7.83	168.65±22.15	1.78±0.22	6.62±0.89	19.52±2.47
T		9.287	7.485	8.894	9.736	6.238
P		<0.05	<0.05	<0.05	<0.05	<0.05

Table 2.
Comparison of peripheral blood immune cells between two groups of patients.

Groups	n	M-MDSC	G-MDSC	Treg	Breg
CRF group	55	5.24±0.78	41.25±5.67	4.49±0.62	5.28±0.71
Control group	82	3.83±0.64	27.38±3.54	3.12±0.45	3.56±0.55
T		7.498	7.117	6.695	7.029
P		<0.05	<0.05	<0.05	<0.05

Table 3.
Comparison of serum tumor markers between two groups of patients.

Groups	*n*	CEA	Cyfra21-1	SCC-Ag	HE4	GDF-15	PCNA
CRF group	55	39.56±5.62	26.51±3.48	3.62±0.62	372.35±47.28	2.15±0.27	0.72±0.09
Control group	82	23.41±3.37	17.45±2.05	2.31±0.36	231.46±32.18	1.25±0.16	0.45±0.06
T		8.289	7.783	7.226	7.528	9.385	8.417
P		＜0.05	＜0.05	＜0.05	＜0.05	＜0.05	＜0.05

Differences in serum CEA, Cyfra21-1, SCC-Ag, HE4, GDF-15 and PCNA levels were statistically significant between two groups of patients ($P<0.05$). Pearson correlation analysis showed that serum CEA, Cyfra21-1, SCC-Ag, HE4, GDF-15 and PCNA levels in CRF group were positively correlated with serum ACTH and TSH levels, and negatively correlated with serum Cor, FT3 and FT4 levels.

4. Discussion

Cancer-related fatigue is a common simultaneous phenomenon in the treatment of malignant tumor, and the appearance of fatigue is closely related to the disorder of endocrine hormones. The hypothalamus-pituitary-adrenal cortex axis is an important endocrine target gland axis that regulates the secretion of glucocorticoids, and the pituitary gland secretes ACTH under the action of hypothalamic hormones and promotes the adrenal cortex to secrete Cor; the Cor that is secreted into the blood circulation can on the one hand, exert the corresponding biological effects, and on the other hand, negatively regulate the synthesis and secretion of ACTH[4]. Cor is the main glucocorticoid in the body, which has a variety of biological activities, and can adjust the material and energy metabolism, increase the tissue sensitivity to catecholamine and affect the immune response and emotional state; when cortisol levels are low, the body is tired and reactively increases ACTH secretion[5,6]. In the study, analysis of serum adrenal cortex-related hormone levels in patients with cancer-related fatigue showed that serum ACTH level of CRF group was significantly higher than that of control group while Cor level was significantly lower than that of control group. This indicates that the changes in hypothalamic-pituitary-adrenal cortex axis function are closely related to the occurrence of cancer-related fatigue.

Thyroid hormone is another important endocrine hormone that affects energy metabolism and emotional state in the body, and it is secreted by the thyroid gland under the action of the pituitary hormone TSH. Excessively synthesized and secreted thyroid hormones in the body can promote the glycogenolysis and increase the basal metabolic rate, and will also cause emotional excitement and hyperactive spirit; but the deficient thyroid hormone synthesis and secretion can lead to lower basal metabolic rate and cause depression and drooping spirit, which can lead to fatigue. Continued hypermetabolism in patients with malignant tumors can lead to excessive consumption of thyroid hormones, which on the one hand, leads to lower thyroid hormone levels, and on the other hand, will reactively increase the synthesis and secretion of pituitary hormone TSH[7,8]. In the study, analysis of serum levels of thyroid-related hormones in patients with cancer-related fatigue showed that serum TSH level of CRF group was significantly higher than that of control group while FT3 and FT4 levels were significantly lower than those of control group. This indicates that the changes of hypothalamic-pituitary-thyroid axis function are closely related to the occurrence of cancer-related fatigue.

Immune escape is the main pathological link in the occurrence and development of malignant tumors, and increase in contents of a variety of inhibitory immune cells can cause antitumor immune response inhibition and increase the risk of immune escape of cancer cells[9]. The persistence of cancer-related fatigue can affect the homeostasis and cause the imbalance of immune response. MDSC is an inhibitory immune cell that is derived from the myeloid cells and can further differentiate into monocytic M-MDSC and granulocyte G-MDSC, which can inhibit the differentiation and maturation of T cells, dendritic cells, NK cells and other immune cells and cause anti-tumor immune response inhibition[10–12]; Treg is a subset in $CD4^+$T cells with immunosuppressive action, which can not only hinder the differentiation of Th1, Th17 and other cells through intercellular contact inhibition, but can also secrete IL-10, TGF-β and other inhibitory cytokines to influence the antitumor immune response[13]; Breg is a subgroup with immunosuppressive activity in B lymphocytes, which can also secrete inhibitory cytokines such as IL-10 and TGF-β and affect immune response[14]. In the study, analysis of peripheral blood contents of inhibitory immune cells in patients with cancer-related fatigue showed that peripheral blood M-MDSC, G-MDSC, Treg and Breg levels of CRF group were significantly higher than those of control group, positively correlated with serum ACTH and TSH levels, and negatively correlated with serum Cor, FT3 and FT4 levels. This indicates that cancer-related fatigue can cause inhibitory immune cell increase and anti-tumor immune response inhibition, and the change of immune response is closely related to the disorder of endocrine hormones.

The serum tumor markers are important indicators to evaluate the changes of malignant tumor, and the increase of tumor load will increase the synthesis and secretion of tumor markers. The change of anti-tumor immune response and the disturbance of endocrine hormones in the patients with cancer-related fatigue can enhance the cancer cell proliferation activity and increase the tumor load. CEA

is the most common marker for screening for malignant tumors, and multiple malignant tumor cells can synthesize CEA[15]; Cyfra21-1 is the product when keratin CK19 falls off, and the CK19 in malignant tumor cells can massively fall off under the action of a variety of proteases and produce Cyfra21-1[16]; both SCC-Ag and HE4 are molecules massively secreted during the malignant transformation and proliferation of squamous epithelial cells[17]; GDF-15 is a molecule that plays a regulatory role in extracellular matrix, which can promote invasion and infiltration of cancer cells[18]; PCNA is the helper protein needed for DNA replication in cells, which is directly related to cell proliferation activity. In the study, analysis of the contents of serum tumor markers in patients with cancer-related fatigue showed that serum CEA, Cyfra21-1, SCC-Ag, HE4, GDF-15 and PCNA levels of CRF group were significantly higher than those of control group, positively correlated with serum TSH and ACTH, and negatively correlated with serum FT3, FT4 and Cor. This indicates that the cancer-related fatigue can increase the tumor marker secretion and the tumor load, and the increase of tumor load is closely related to the disorder of endocrine hormones.

To sum up, it is believed that the occurrence of cancer-related fatigue is related to the changes in thyroid hormone and adrenal cortical hormone levels; the disorder of endocrine hormone can result in anti-tumor immune response inhibition and tumor load increase.

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