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The Relationship Between T Lymphocyte Subsets and TPOAb & TGAb Levelin Patients with Hashimoto's Thyroiditis

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Abstract: Background: Hashimoto's Thyroiditis is a common autoimmune thyroid disease of organ specificity mediated by T cells, the abnormal activation of auto-reactive T cells has close relation with the attack of HT and participates in the attack process of HT. TPOAb and TGAb is important symbols of HT thyroiditis. Most of patients have continuous TPOAb and TGAb level rise. Objective: To assess the relationship between T Lymphocyte Subsets and TPOAb & TGAb Level in Patients with Hashimoto's Thyroiditis. Method: 130 clinically diagnosed HT patients are selected as the study object and were divided into high level group and low level group (with 65 cases for each group) as per the expression condition of TPOAb and TGAb; another 40 healthy check-up people are selected as the control group. Flow cytometry is adopted to test the T lymphocyte subsets, and ELISA is adopted to test Th1 cytokine (IL-2, IFN-γ) and Th2cytokine (IL-4, IL-10). Result: $CD3^+T$, $CD3^+CD4^+T$ and $CD4^+/CD8^+$ of high level TPOAb group and high level TGAb group are obviously higher than that of low level group and the control group, $CD3^+CD8^+T$ is obviously lower than that of low level group and the control group; the $CD3^+CD4^+T$ of the low level TPOAb group and low level TGAb group is obviously higher than the control group, which has statistic meaning ($P<0.05$). IL-2 and IFN-γ of the high level TPOAb group and high level TGAb group is obviously lower than the low level group while higher than the control group, and the IL-4 and IL-10 is obviously higher than the low level group and the control group; the IL-2 and IFN-γ of the low level TPOAb group and low level TGAb is obviously higher than that of high level group and the control group, and the IL-4 and IL-10 is obviously lower than that of the high level group and the control group, and the differences all have statistic meaning ($P<0.05$). Correlation analysis indicates that TPOAb and TGAb are in positive correlation with $CD3^+CD4^+T$ and $CD4^+/CD8^+$, while in negative correlation with $CD3^+CD8^+T$. Conclusion: T lymphocyte subsets in the HT patients have obvious correlation with the level of TPOAb and TGAb, and may have close relationship with the occurrence and development of HT.

Keywords: Hashimoto's Thyroiditis, TPOAb, TGAb, T Lymphocyte Subsets, Cytokines

1. Introduction

Hashimoto's Thyroiditis (HT) is a common clinical autoimmune thyroid disease, and its occurrence has close relationship with cellular immunity and humor immunity dysfunction of organism [1], it was characterized by lymphocyte infiltration, production of autoantigen-specific T lymphocytes and increase of specific thyroid antibody [2, 3]. The patient's auto-reactive T cell is activated [4], T suppressor cell (Ts) gets abnormal and allows helper T cell (Th) and antigen to interact, which causes damage to thyroid tissue. In HT patients, the number of helper T cells increased, the number of inhibitory T cells decreased, and the ratio of helper T cells to inhibitory Tcells increased [5], at the same

time, the proportion of Th1/Th2 cells was unbalanced. Th1 cells played a leading role in the pathogenesis of HT, while Th2 cells played a protective role [6-9]. Most of the HT patients have continuous rise of Thyroid peroxidase antibody (TPOAb) and Thyroglobulin antibody (TGAb) level, which is the one of main bases for HT diagnosis [10]. It has been found that TPOAb and TGAb can affect the synthesis of thyroid hormone and cause damage to thyroid cells [11, 12]. It has important significance for prognosis of HT to identify the severity of the disease at the early stage, the value of TPOAb and TGAb in HT diagnosis has been recognized, but there are few reports on the relationship of their expression with the state of HT, especially with the dysfunction of cell immunity. By analyzing the relationship between T lymphocyte subsets and TPOAb &TGAb in Patients with Hashimoto's Thyroiditis, this paper aims at discussing the inner relationship of TPOAb and TGAb level with the patient's cell immunity function.

2. Methods

2.1. General Information

130 patients who were clinically diagnosed with HT in the endocrinology department of Cangzhou Hospital of Integrated Traditional Chinese and Western Medicine, Hebei province from October, 2017 to March, 2019 were chosen to be study objects, among which there were 26 men cases, 104 women cases with age from 21~67, and the average age were (44.15±18.69) years old.

They were divided into high level group and low level group (with 65 cases for each group) as per the expression condition of TPOAb and TGAb. Besides, 40 healthy check-up people are selected as the control group, in which there were 8 men cases and 32 women cases with age from 22~67, and the average age were (45.33±16.48) years old. This research has been approved by the ethics committee and all the subjects were informed and agreed.

2.2. Diagnostic Criteria and Exclusion Criteria

2.2.1. Diagnostic Criteria

Refers to the diagnostic criteria in the 8th version of Internal Medicine published by the People's medical publishing house [13], including: (1) the one with typical clinical features, such as diffusing goiter, tough texture, especially with thickening of isthmus and pyramidal lobe, etc., or TPOAb or TGAb positive; (2) the one without goiter, but with distinct TPOAb or TGAb increase as well as hypothyroidism.

2.2.2. Exclusion Criteria

(1) With the history of pituitary or hypothalamus disease; (2) Taked medicine which affects thyroid function; (3) Patient with autoimmune diseases; (4) The pregnant or breastfeeding woman; (5) Patient with abnormal liver and kidney function, and/or cardiac insufficiency; (6) Patient without complete clinical date.

2.3. Experimental Method

2.3.1. Specimen Collection

Morning fasting venous blood is taken from all the examinees and put into pro-coagulation tube with separating glue and EDTA-K2 anticoagulant tube. Serum is separated from the pro-coagulation tube with separating glue timely for testing TPOAb and TGAb. The specimen in the EDTA-K2 anticoagulant tube is shaken evenly, without centrifugation, for testing T lymphocyte subsets with the whole blood.

2.3.2. TPOAb and TGAb Test

Adopt Cobas E 601 electro generated chemiluminescence analyzer of Roche to test TPOAb and TGAb, all the reagents are corollary reagents of instrument companies.

2.3.3. The Testing of T Lymphocyte Subsets

Flowcytometry FACSCalibur provided by American BD company is adopted to test T lymphocyte subsets, and all the reagents are corollary reagents of instrument companies. The test items included: the percentages of $CD3^+T$, $CD3^+CD4^+T$, $CD3^+CD8^+T$ and the ratio of $CD4^+/CD8^+$.

2.3.4. Cytokines Test

Adopt ELISA double antibody sandwich method to test Th1 type cytokines (IL-2 and IFN-γ) and Th2 cytokines (IL-4 and IL-10), with the assays purchased from MultiSciences (Lianke) Biotech Co., Ltd. and the operation conducted strictly in accordance with the instruction manual.

2.4. Statistic Method

The data adopts SPSS24.0 software for analysis and processing, the metering data is expressed by ($\bar{x} \pm s$), the comparison among multiple groups adopts analysis of variance, pairwise comparison adopts SNK-q test, and correlation analysis adopts linear correlation analysis.

3. Results

3.1. Comparison of T Lymphocyte Subgroups Between High and Low Level TPOAb Groups

$CD3^+T$, $CD3^+CD4^+T$ and $CD4^+/CD8^+$ of high level TPOAb group are obviously higher than that of low level group and the control group, $CD3^+CD8^+T$ is obviously lower than that of low level group and the control group, and the difference has statistic significance ($P<0.05$); the $CD3^+CD4^+T$ of the low level TPOAb group is obviously higher than the control group, and the difference has statistic significance ($P<0.05$), as for the $CD3^+T$, $CD3^+CD8^+T$, $CD4^+/CD8^+$, the comparison of the low level TPOAb group with the control group, the difference has no statistic significance ($P>0.05$). (Table 1)

Table 1. *Comparison of T lymphocyte subgroups between high and low level TPOAb groups.*

Groups	n	$CD3^+T$ (%)	$CD3^+CD4^+T$ (%)	$CD3^+CD8^+T$ (%)	$CD4^+/CD8^+$
high level TPOAb group	65	70.89±8.23	45.17±8.49	24.46±6.81	1.94±0.91
low level TPOAb group	65	68.85±9.26	42.38±8.72	26.45±6.54	1.63±0.83
Normal control group	40	68.73±9.72	40.14±9.34	27.03±5.83	1.58±0.62
F		5.724	10.461	6.582	11.314
P		0.042	0.017	0.036	0.014

3.2. Comparison of T Lymphocyte Subgroups Between High and Low Level TGAb Groups

$CD3^+T$, $CD3^+CD4^+T$ and $CD4^+/CD8^+$ of high level TGAb group are obviously higher than that of low level group and the control group, $CD3^+CD8^+T$ is obviously lower than that of low level group and the control group, and the difference has statistic significance ($P<0.05$); the $CD3^+CD4^+T$ of the low level TGAb group is obviously higher than the control group, and the difference has statistic significance ($P<0.05$), as for the $CD3^+T$, $CD3^+CD8^+T$, $CD4^+/CD8^+$, the comparison of the low level TGAb group with the control group, the difference has no statistic significance ($P>0.05$). (Table 2)

Table 2. *Comparison of T lymphocyte subgroups between high and low level TGAb groups.*

Groups	n	$CD3^+T$ (%)	$CD3^+CD4^+T$ (%)	$CD3^+CD8^+T$ (%)	$CD4^+/CD8^+$
high level TGAb group	65	70.17±9.04	44.98±8.53	24.32±7.01	1.91±0.89
low level TGAb group	65	68.94±8.47	42.57±8.63	26.43±6.62	1.65±0.86
Normal control group	40	68.73±9.72	40.14±9.34	27.03±5.83	1.58±0.62
F		5.417	9.714	7.136	10.327
P		0.043	0.020	0.031	0.018

3.3. Comparison of Cytokines Between High and Low Level TPOAb Groups

IL-2 and IFN-γ of the high level TPOAb group is obviously lower than the low level group while higher than the control group, and the IL-4 and IL-10 is obviously higher than the low level group and the control group; the IL-2 and IFN-γ of the low level TPOAb group is obviously higher than that of high level group and the control group, and the IL-4 and IL-10 is obviously lower than that of the high level group and the control group, and the differences all have statistic meaning ($P<0.05$). (Table 3)

Table 3. *Comparison of cytokines between high and low level TPOAb groups (pg/ml).*

Groups	n	IL-2	IFN-γ	IL-4	IL-10
high level TPOAb group	65	2.62±1.73	4.05±3.24	3.46±2.03	2.99±2.27
low level TPOAb group	65	3.85±2.75	6.24±5.13	2.21±1.76	1.88±1.41
Normal control group	40	2.08±0.93	3.25±2.12	2.83±1.56	2.63±1.94
F		6.125	8.725	5.613	4.798
P		0.026	0.009	0.031	0.042

3.4. Comparison of Cytokines Between High and Low Level TGAb Groups

IL-2 and IFN-γ of the high level TGAb group is obviously lower than the low level group while higher than the control group, and the IL-4 and IL-10 is obviously higher than the low level group and the control group; the IL-2 and IFN-γ of the low level TGAb group is obviously higher than that of high level group and the control group, and the IL-4 and IL-10 is obviously lower than that of the high level group and the control group, and the differences all have statistic meaning ($P<0.05$). (Table 4)

Table 4. *Comparison of cytokines between high and low level TGAb groups (pg/ml).*

Groups	n	IL-2	IFN-γ	IL-4	IL-10
high level TGAb group	65	2.70±1.79	4.13±3.75	3.33±2.10	2.96±2.17
low level TGAb group	65	3.79±2.71	6.17±5.06	2.29±1.83	1.92±1.48
Normal control group	40	2.08±0.93	3.25±2.12	2.83±1.56	2.63±1.94
F		5.926	8.362	5.143	5.012
P		0.029	0.011	0.037	0.038

3.5. Correlation Between TPOAb, TGAb and T Lymphocyte Subgroups

TPOAb and TGAb are in positive correlation with $CD3^+CD4^+T$ ($r=0.436$, $p=0.017$; $r=0.393$, $p=0.030$) and $CD4^+/CD8^+$ ($r=0.492$, $p=0.006$; $r=0.446$, $p=0.012$), while in negative correlation with $CD3^+CD8^+T$ ($r=-0.395$, $p=0.026$; $r=-0.382$, $p=0.034$).

4. Discussions

T cell is a kind of important leukomonocyte for mediating

cell immune response and regulating organism immunity function. CD4 molecule of Th expression is the main cell group of $CD4^+$T. As per the difference of the cytokine it secretes, Th cell can also be divided into Th1 cell and Th2 cell; Th1 cell mediates the cell immune response by releasing IL-2, IFN-γand other cytokines while Th2 cell promotes B cell to be activated and generate antibody by releasing IL-4, IL-10 and other cytokines [14]. $CD8^+$T cell includes not only cytotoxic T cells but also Ts. The latter mainly suppresses the proliferation of self T lymphocytes to the antigen and suppresses B cell to generate antibody. Under normal conditions, various lymphocyte subsets maintain balanced, interact, and maintain the normal immune function of the body [15].

Hashimoto's Thyroiditis is a common organ specific autoimmune disease mediated by T cells, the change of T cell subset has close relationship with the occurrence of HT [16], the auxiliary T cells in the patients' body are relatively active, suppressor T cells reduce in quantity and has function defect [17]. By comparing the change conditions of the percentage of T lymphocyte subsets with different level of antibody, this paper discovers that the percentage of Th cell of high level TPOAb group and high level TGAb group is obviously higher than that of low level group and the control group, while the percentage of Ts cell is obviously lower than low level group and the control group; compared the low level TPOAb group and low level TGAb group with the control group, the percentage of Th cell has obvious rise while the percentage of Ts cell doesn't have obvious change, which explains that at the stage with relatively low antibody level, the patient has relatively active Th cells, and with the rise of the antibody, such a phenomenon is even more obvious. At the early stage of HT, Th cells have invaded in the thyroid tissue widely and cause damage to the thyroid tissue by releasing various inflammatory cytokines, and are the main invasive cells of thyroid cells at the early stage [18]. With the development of the disease, T lymphocytes increase, and the percentage of Th cell in the patient constantly rises, but the percentage of Ts cells which has suppression function reduces; while the Th cells have active function, the patient has the relative defect of Ts cell function, the immunity suppression function is relieved and a lot of lymphocytes, NK cells, plasma cells and macrophages invade, which causes damage to the thyroid tissue [19, 20]. TPO and TG will have continuous stimulation function on B lymphocytes, and the level of TPOAb and TGAb rises constantly [21]. By analyzing the correlation between TPOAb & TGAb and T lymphocytes subset in the patients, this paper indicates that Th cell is in positive correlation with TPOAb and TGAb level, while Ts cell is in negative correlation with TPOAb and TGAb level; with the development of the disease, the imbalance of T lymphocyte subset gets even more obvious; the rise of Th cells and the drop of Ts cells will make the TPOAb and TGAb level rise continuously. After combining with corresponding antigen, TPOAb and TGAb can further damage thyroid follicular membrane by activating complement and the cytotoxic effect mediated by the cell which the and antibody depend on, and cause apoptosis of thyroid cells in return [22, 23], and make the patients' disease more severe.

The balance of Th1/Th2 plays an important role in the stability of organism immunity function, and the imbalance may cause disease mediated by immunity. Research discovers that HT patients have the disorder of Th1 /Th2 cell balance, Th1/Th2cytokines participate in the attack and development of HT [24], most researches believe that HT patients'Th1/Th2 cell balance deviates toward Th1, and some researches also believe that HT patients' Th cell imbalance deviates toward Th2 [6]. By comparing Th1 cytokines (IL-2 and IFN-γ) and Th2 cytokines (IL-4 and IL-10) of TH patients with different antibody level, this paper discovers that the Th1 cytokines of low level TPOAb group and low level TGAb group are obviously higher than that of the high level group and the control group, and Th2 cytokines are obviously lower than the high level group and the control group; Th1 cytokines of high level TPOAb group and high level TGAb group is obviously higher than the control group, but lower than the low level group, and the Th2 cytokines are obviously higher than the low level group and the control group. It is deduced that the risen Th cells of the low level antibody group are mainly Th1 cells, while the risen Th cells of the high level antibody group are mainly Th2 cells; considering that, at different stage of the disease, Th1 /Th2 cell balance has differences, at the early stage, Th1 cells invade the thyroid tissue widely and increase the expression of HLA-II molecules of thyroid epithelial cells by secreting IFN-γ and other cytokines, which makes the thyroid cells turn into antigen presenting cells, makes the Th lymphocytes to secrete and release IL-2, and promotes the expression of IL-2 receptors on the cell surface; the combination of IL-2 and IL-2 receptor can activate Th lymphocytes to secrete other cytokines and make a lot of T lymphocytes and monocytes enter into the thyroid through Chemotaxis, which causes damage to the thyroid directly [25, 26]. With the development of the disease, affected by multiple factors of the organism, Th1/Th2 cell balance deviates toward Th2 cells, under the function that Th2 cytokines promote the generation of antibody, the TPOAb and TGAb level in the patient's body rises continuously, which further deteriorates the damage to thyroid cells.

5. Conclusions

All in all, the imbalance of T lymphocyte subset in the HT patients is expressed as the hyperfunction of Th cells and relative defect of Ts cells. HT patients with different antibody level all have Th cell rise, and the rise degree is in positive correlation with the antibody level; the Th cell of the low level antibody group is mainly Th1 cell, while both the Th1 cell and Th2 cell of the high level antibody group rise, with the balance deviating toward Th2 cell; the percentage of Ts cell is in negative correlation with the antibody level, the change of the low level antibody group is not obvious, and there is obvious drop for high level antibody group. The imbalance of T lymphocyte subset has obvious difference in HT patients with different antibody level, and may have close relationship with the occurrence and development of HT.

6. Future Work

Real time monitoring of the relationship between T lymphocyte subsets and antibody levels and thyroid function in patients with HT, to clarify the influence of immune status on thyroid function, and to provide new ideas for further study of pathogenesis and clinical treatment of HT.

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