

# The clinical and immunological features of bronchial asthma in patients with autoimmune thyroiditis

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Bronchial asthma often can be combined with autoimmune thyroiditis, and both diseases are linked with the immune system dysfunction, although *via* different pathogenetic mechanisms, but intermingled. In this study the clinical course of bronchial asthma, respiratory function, immune and hormonal status in patients with bronchial asthma and autoimmune thyroiditis were compared to those in patients with pure bronchial asthma without thyroid disease. Along with the marked changes in cellular and humoral components of the immune system, clinical observations showed that the addition of autoimmune thyroiditis to bronchial asthma worsens asthma course: it leads to an increase in the frequency of exacerbations, shortening the duration of remission, a significant decrease in the flow rates of MEF50 and MEF75 compared with isolated bronchial asthma, probably, related to myxoedematous component of bronchial conductivity impairment.

*Keywords:* bronchial asthma, autoimmune thyroiditis, immune status, cytokines.

Bronchial asthma (BA) is a heterogeneous disease, in which the outcome and prognosis both depends on many factors, including comorbidity [1]. BA often can be combined with autoimmune diseases of the thyroid gland [2].

Autoimmune thyroiditis (AIT) is a chronic inflammatory disease of the thyroid gland (TG) of autoreactive origin, in which a chronically progressive lymphoid infiltration causes a gradual destruction of thyroid tissue, if untreated most often leading to the development of primary hypothyroidism. Diagnostic criteria for autoimmune thyroiditis include: increased circulating thyroid autoantibodies (to thyroperoxidase and to thyroglobulin), detection of typical AIT ultrasound image, primary hypothyroidism (overt or subclinical) [3].

## Aim

Comparative study of the clinical course of BA, respiratory function (RF), immune and hormonal status — in patients with BA in combination with autoimmune thyroiditis (AIT) compared to patients with pure BA without thyroid disease.

## Materials and methods

56 patients with BA were examined. They were divided into two groups: *group 1* (n=26) consisting of patients with BA with autoimmune thyroiditis (BA + AIT) (women, mean age  $57.0 \pm 16.2$  years), *group 2* (n=30) — patients with isolated BA (women, mean age  $54.2 \pm 8.0$  years). Control group consisted of 30 healthy volunteers without any pathology of respiratory system and/or thyroid gland. Patients with BA (n=56) received basic therapy with inhaled glucocorticosteroids in an average dose. Patients with BA + AIT (n=26) were diagnosed with AIT taking into account common diagnostic criteria [3]. They received replacement therapy with L-thyroxine in a medium dose (in average:  $75.5 \pm 24.4$   $\mu\text{g}/\text{day}$ ). The clinical picture was assessed by the dynamics and severity of breath shortage, presence of day and night attacks of suffocation; cough, sputum expectoration and its nature, and hoarseness of voice. All patients underwent spirometry according to criteria of BA diagnosis verification [4], as well as the series of immunological tests (measurements of serum concentrations of IL-1 $\beta$ , IL-4, IL-6, INF $\gamma$ , IgE total, Ig A, Ig G, and determination of lymphocyte subpopulations share). Immunoendocrinological tests included: determination of thyroid-stimulating hormone blood concentration (TSH), thyroid hormones (T3 and T4), and autoantibodies to thyroid peroxidase (anti-TPO). Statistical data processing was performed using the Statistica 7.0 software package.

## Results and discussion

In 15 (57.7%) patients with BA + AIT, the leading complaint was a low-yielding cough, not associated with contact with cause-significant allergens. Among the provoking factors of exacerbation of BA + AIT, viral infections prevailed. Analysis of the frequency of exacerbations of BA + AIT (anamnestic data for the previous 12 months) showed that the addition of AIT to BA increases the frequency of exacerbations of BA ( $6.2 \pm 0.3$  times a year compared with  $4.5 \pm 0.6$  times a year;  $p=0.04$ ). When assessing the duration of BA remission, it was found that the appearance of concomitant pathology — AIT — significantly shortened the duration of BA remission ( $8.6 \pm 0.9$  weeks in the BA + AIT group and  $9.3 \pm 0.4$  weeks compared to  $12.1 \pm 0.8$  weeks in the BA group;  $p=0.02$  and  $p=0.03$ , respectively).

The study of RF in patients with BA (1 and 2 groups) revealed no statistically significant differences in FEV1 ( $66.21 \pm 2.04$ ;  $66.52 \pm 2.41$ ; control  $82.02 \pm 1.35$ ;  $p=0.02$ ). However, between groups BA and BA + AIT significant differences of flow indicators, MEF50, MEF75 were detected. Patients from the group of BA + AIT compared with the BA group showed lower values MEF50 ( $48.91 \pm 3.02$ ;  $60.62 \pm 2.53$ ; control of  $82.02 \pm 1.35$ ;  $p=0.02$ ) and MEF75 ( $35.24 \pm 1.78$ ;  $48.74 \pm 1.78$ ; control  $80.42 \pm 2.01$ ;  $p=0.02$ ).

Evaluation of the immune status of patients revealed changes in cellular and humoral components of the immune system in patients with BA + AIT in comparison with cases of isolated BA and with control as well. Patients of group 1 (BA + AIT) showed an increase in the percentage of mature lymphocytes (CD3+, %,  $83.3 \pm 2.0$ ; 2 gr.  $66.2 \pm 3.2$ ; control  $71.3 \pm 1.5$   $p < 0.05$ ); significant increase in the content of lymphocytes with helper-inducor activity (CD4+, %,  $52.6 \pm 2.7$ ; 2 gr.  $44.2 \pm 2.3$ ; control  $40.7 \pm 1.2$   $p < 0.05$ ); but reduction of suppressor cytotoxic subpopulation percentage (CD8+, %,  $18.1 \pm 1.8$ ; 2 gr.  $20.2 \pm 3.2$ ; control  $20.7 \pm 1.3$   $p < 0.05$ ), which caused an increase in the immunoregulatory index

(CD4+/CD8+,  $2.9 \pm 0.7$ ; 2 gr.  $1.9 \pm 0.2$ ; control  $2.0 \pm 0.4$   $p < 0.05$ ). An increase in the relative number of natural killers (CD16+, %,  $16.4 \pm 1.8$ ; 2 gr.  $10.4 \pm 1.2$ ; control  $12.7 \pm 1.1$   $p < 0.05$ ) was revealed. Regarding the humoral link of immunity: an increase in share of B-lymphocytes was noticed (CD19+, %,  $16.3 \pm 2.0$ ; 2 gr.  $15.6 \pm 1.4$ , control  $10.3 \pm 1.5$   $p < 0.05$ ), which was accompanied by a significant increase in content of Ig A (g/l,  $1.40 \pm 0.01$ ; 2 gr.  $1.01 \pm 0.03$ ; control  $0.98 \pm 0.02$   $p = 0.02$ ), IgG (g/l,  $16.10 \pm 1.42$ ; 2 gr.  $12.09 \pm 1.14$ , control  $12.3 \pm 1.5$   $p = 0.02$ ), as well as in concentration of circulating immune complexes (u.e.,  $120.0 \pm 1.2$ ; 2 gr.  $60.30 \pm 5.3$ ; control  $58.04 \pm 2.6$   $p < 0.05$ ). The level of autoantibodies to thyroid antigen (TPO) also was elevated (IU/ml,  $1175.2 \pm 206.9$ ; 2 gr.  $30.1 \pm 12.0$ ; control  $30.4 \pm 10.4$   $p < 0.005$ ), which makes an additional contribution to the development of the pathological process, exacerbating the destruction of thyroid tissue with the subsequent development of hypothyroidism. When determining the concentration of total IgE in serum, the maximum values were obtained in the group of isolated BA compared to the groups of BA + AIT and to controls (IU/ml,  $259.4 \pm 3.8$ ;  $122.5 \pm 9.8$ ;  $78.4 \pm 5.6$   $p = 0.01$ , respectively). At the same time assessing the level of thyroid hormones (T3, nmol/l (BA + AIT  $1.004 \pm 0.07$ ; BA  $1.48 \pm 0.13$ ; control  $1.98 \pm 0.02$   $R < 0.001$ ); T4, units (BA + AIT  $9.07 \pm 0.32$ ; BA  $21.87 \pm 0.43$ ; control  $23.2 \pm 0.97$   $R < 0.001$ )) and TSH (mU/l, BA + AIT  $9.07 \pm 1.22$ ; BA  $380 \pm 0.09$ ; control  $< 3.41 \pm 1.9$  —  $p < 0.001$ ) we revealed a decrease in thyroid function among patients with BA + AIT. This is confirmed by the data of other researchers [5], which showed that a long deficiency of thyroid hormones reduces the production of total IgE.

The cytokine status of the patients had some features: patients with BA + AIT had a maximum value of levels of IL-1 $\beta$  compared to patients from group BA and to the control (PG/ml,  $18.14 \pm 0.82$ ;  $8.30 \pm 0.21$ ;  $5.24 \pm 2.18$  respectively,  $p = 0.0001$ ), IFN- $\gamma$  (PG/ml,  $275.02 \pm 6.63$ ;  $93.58 \pm 1.78$ ,  $12.74 \pm 1.51$   $p = 0.00013$ ), and IL-6 (PG/ml, of  $39.64 \pm 3.72$   $30.5 \pm 0.72$ , of  $6.80 \pm 2.04$ ,  $p = 0.0011$ ). This indicates in favor of high activity of Th1-dependent reactions in AIT, and may be explained by excessive secretion of IL-6 by thyrocytes under the influence of proinflammatory factors, during destructive processes in the thyroid tissue. At the same time, there was an increase in serum concentrations of IL-4 in patients with BA in comparison with patients from the BA + AIT group and controls (PG/ml,  $254.42 \pm 4.49$ ;  $180.75 \pm 19.20$ ;  $4.42 \pm 2.06$   $p = 0.004$ , respectively). From these indicators it follows that BA + AIT is characterized by significantly lower activity of Th2-dependent immunological reactions compared with BA.

## Conclusion

Along with the marked changes in immunological reactions, clinical observations show that the addition of autoimmune thyroiditis to BA worsens asthma course: it leads to an increase in the frequency of exacerbations, shortening the duration of remission, a significant decrease in the flow rates of MEF50 and MEF75 compared with isolated BA, probably, related to myxoedematous component of bronchial conductivity impairment.

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