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ORIGINAL ARTICLES

Hyperthyroidism and Asthma

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Key words: Hyperthyroidism; Asthma

ABSTRACT

Two patients presented with new onset of thyrotoxicosis and they then developed episodic wheezing a few months afterward. The asthmatic attacks improved when the patients were rendered in a euthyroid state with treatment. The present paper discusses the relationship between two diseases, hyperthyroidism and asthma, and the underlying factors potentially contributing to their conditions. The present findings suggest that asthma may develop in a susceptible individual with hyperthyroidism and it is possible that the reactive oxygen species may be a contributory factor in exacerbating wheezing in our hyperthyroid patients.

INTRODUCTION

Thyroid and lung diseases occasionally occur together. An interaction between these two diseases has been recognized in the literature (1–4). Asthma usually deteriorates when hyperthyroidism develops, and it improves when patients are rendered in euthyroid states. Bush

et al. (5) found a remarkable improvement in asthma with the development of hypothyroidism. Conversely, the treatment of hypothyroidism may result in the worsening of asthma (6,7). The present paper reports the occurrence of asthma in hyperthyroid patients and discusses the underlying factors potentially contributing to the association of the conditions.

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CASE PRESENTATION

Case No. 1

A 44-year-old Vietnamese female presented with weight loss (12 lb in 6 months), nervousness, heat intolerance, tremor, and an enlarged neck. Her past medical history was unremarkable. On the physical examination, she had a pulse rate of 100 beats/min, a diffuse enlargement of thyroid gland, a fine tremor in both hands, and a hyperreflexia of the extremities. The laboratory data were as follows: triiodothyronine uptake (T_3U), 41% (normal, 22%–37%); thyroxine by radioimmunoassay (T_4RIA), 19.9 $\mu\text{g}/\text{dL}$ (normal, 5–15); triiodothyronine by radioimmunoassay (T_3RIA), 409 ng/dL (normal, 86–187); free thyroxine index (FTI), 8.2 (normal, 1.5–4); thyroid-stimulating hormone (TSH), <0.1 mIU/mL (normal, 0.2–5); antimicrosomal antibodies (AMA), <0.1 U/mL (normal, <0.3); serum thyroglobulin level, 28 ng/mL (normal, 0–60). The ultrasonography of thyroid gland revealed a homogenous thyromegaly (right lobe, $5.7 \times 1.6 \times 2.5$ cm and left lobe, $5.2 \times 1.7 \times 2$ cm) and no focal nodule. She was treated with propylthiouracil (PTU) 100 mg, twice a day.

Two months later, she experienced episodic wheezing and dyspnea. Her thyroid function tests were as follows: T_3U , 44.9%; T_4RIA , 10.9 $\mu\text{g}/\text{dL}$; T_3RIA , 240 ng/dL ; FTI, 4.9; and TSH, 0.02 mIU/mL . The pulmonary function tests showed an airflow obstruction with forced vital capacity (FVC) of 2.29 L (92.1% predicted) and forced expiratory volume in 1 sec (FEV_1) of 1.92 L (90.7% predicted). There was a partial reversal of the airway obstruction following use of the bronchodilator. She started taking oral theophylline and inhaled β_2 -agonist medications. Her asthma attacks relapsed a few months later, and she required hospitalization. However, her asthma improved when she was rendered in a euthyroid state.

Case No. 2

The patient was a 34-year-old Vietnamese woman who complained of weight loss (16 lb in 6 months), nervousness, temperature intolerance, and fatigue. Her past medical history was remarkable for goiter and a benign ovar-

ian cyst had been removed. On the physical examination, she had a heart rate of 90 beats/min, a diffuse enlargement of the thyroid gland, and a hyperreflexia of the extremities. The laboratory examination data were as follows: T_3U , 49.1%; T_4RIA , 20 $\mu\text{g}/\text{dL}$; FTI, 9.8; T_3RIA , 718 ng/dL ; TSH, <0.1 mIU/mL ; AMA, 1.4 U/mL ; and anti-thyroglobulin antibodies, 1.8 U/mL (normal, <0.1). The ultrasonography of thyroid gland showed a homogenous thyromegaly (left lobe, $5.5 \times 1.9 \times 2.1$ cm and right lobe, $5.5 \times 1.8 \times 2.4$ cm). The thyroid scan and uptake studies suggested hyperthyroidism (6-hr uptake, 46.6% and 24-hr uptake, 48.5%). She was treated with PTU 300 mg twice a day.

Two months later, she developed episodic wheezing and nonproductive coughs. Her thyroid function tests were as follows: T_3U , 40.4%; T_3RIA , 342 ng/dL ; T_4RIA , 17.1 $\mu\text{g}/\text{dL}$; FTI, 6.9; and TSH, 0.1 mIU/mL . Her pulmonary function tests showed an airway obstruction (FVC of 2.05 L or 94% predicted, and FEV_1 of 1.33 L or 68% predicted) and there was a reversibility of the airway obstruction following use of the bronchodilator. She was managed with oral theophylline and inhaled β_2 -agonist medications. The asthmatic attacks, however, improved when she was rendered in a euthyroid state.

DISCUSSION

The relationship between the respiratory system and thyroid gland has been well-documented in the literature. Walezynski (8) found a greater incidence of goiter in asthmatic children (28%) when compared with the control group (10%). In 1917, Peabody and Wentworth (9) first noted a reduction of vital capacity (VC) in hyperthyroid patients. They found that some of their patients had a VC less than 80% of the predicted normal. The reduced VC was reversible with treatment, and it was associated with a reduction of maximum inspiratory pressure (10–12). This reduction, however, was attributed to respiratory muscle weakness. Harrison and Tattersfield (13) reported an inverse relationship between the airway adrenergic responsiveness and the level of thyroid function; the airway response to sal-

butamol was reduced in thyrotoxic subjects before treatment. Cockcroft et al. (14) noted a decrease in the nonspecific bronchial reactivity in an asthmatic patient after treatment for hyperthyroidism. Irwin et al. (15), however, observed that T_3 -induced thyrotoxicosis had no effect on the airway reactivity or lung function in normal volunteers. This study, however, used only a 3-week treatment period that might not be long enough to induce the thyrotoxic change in the airway (16). Roberts et al. (16) found no significant change in bronchial reactivity in a group of nonasthmatic patients after treatment for hyperthyroidism. Kendrick et al. (17) reported a lack of change in bronchial reactivity to methacholine in a similar group of patients. In addition, the effects of thyroid hormone on airway reactivity may be different in normal subjects and asthmatic patients. On the other hand, Ismail et al. (18) reported that T_3 ameliorated cases of chronic asthma. Furthermore, Nakazama and Kobayashi (19) found no apparent uniform influence on the severity of asthma in patients with both diseases.

These findings suggested that even if hyperthyroid patients were at risk of developing asthma, hypothyroidism might reduce the risk of asthma development. Fedrick and Baldwin (20) reviewed the records of 890 hyperthyroid patients and found only one asthmatic patient; notably, the expected number of persons to have this association was 0.9. Two asthmatic patients were found in 316 hypothyroid patients and the expected number of persons with this combination was 0.27. In addition, Schwartz (21) studied 99 patients with allergic rhinitis and/or allergic asthma and he did not find any increase in incidence of thyroid dysfunction. These observations may suggest that asthma develops only in some susceptible hyperthyroid patients.

The pathogenic mechanisms of the exacerbation of asthma were discussed in previous publications. It was suggested that the excess thyroid hormone might have influence on asthma either by altering cellular levels of cyclic nucleotides, altering the sympathetic nervous system activity, increasing the rate of corticosteroid metabolism, or potentiating the prostaglandin's direct effect on airways.

First, Settiple et al. (2) suggested that

there might be a decrease in intracellular levels of cyclic adenosine 3'5'-monophosphate (AMP) in hyperthyroidism. This decrease may further aggravate the already malfunctioning adenylyl cyclase system, which can be found in asthmatic patients (22). However, the results of studies on the cyclic 3'5'-AMP levels in hyperthyroidism did not support such a hypothesis. Karlberg et al. (23) showed that cyclic 3'5'-AMP levels in plasma, adipose tissue, and skeletal muscle in hyperthyroid patients were significantly higher than those in normal subjects. In addition, the infusion of epinephrine caused a greater increase in urinary cyclic 3'5'-AMP in thyrotoxic patients than in control subjects (24).

Second, some evidence suggested that thyrotoxicosis worsens asthma because of either a change in the levels of catecholamines and/or a reduction in the endogenous beta-sympathetic activity. Some authors (25,26) found normal or low circulating catecholamine levels and catecholamine secretion rates in hyperthyroid patients. The tissue responsiveness to catecholamines, however, is increased by thyroid hormones, and hyperthyroid patients are much more sensitive than usual to catecholamines (27), and such patients improve with beta-adrenergic-blocking medications (28). Accordingly, these results should be a benefit to patients with asthma, but the onset of thyrotoxicosis in asthmatic patients is often heralded by the development of side effects from the usual doses of sympathomimetic medications (2,29).

Third, the altered corticosteroid metabolism has been suggested as a possible mechanism whereby hyperthyroidism could result in the worsening of the asthma (5). Hellman et al. (30) reported that an elevated level of thyroid hormone, either by the administering of T_3 or by spontaneous hyperthyroidism, caused a pronounced alteration in hydrocortisone metabolism to its inactive 11-ketonic metabolites, together with an absolute increase in the endogenous production of adrenal hormone. The onset of hyperthyroidism has been found to increase steroid requirements for the treatment of established asthma (2). The significance of these changes regarding asthma is uncertain. Bush et al. (5) suggested that hyperthyroidism might cause asthma by altering the

active circulating cortisol levels; a decrease in circulating cortisol levels should diminish the sensitivity of adrenergic receptors. There is some evidence that asthmatic patients display a reduction of beta-adrenergic response and that this reduction is aggravated when beta₂-agonist bronchodilator therapy is administered (31). Thyrotoxic patients, however, are extremely sensitive to adrenergic drugs (27). In addition, Peterson (32) found normal plasma cortisol levels in most hypo- and hyperthyroid patients.

Finally, Hoult and Moore (33) suggested that potentiating of prostaglandin's (PG) direct actions on airways, as a result of the decrease in pulmonary PG metabolism consequent to hyperthyroidism, might cause the worsening of the asthma. They showed that the breakdown of PGE₂ and PGF₂ (which are bronchoconstrictors) in vitro by lungs and kidneys of hyperthyroid rats is reduced by a mean of 49% (33–35) when compared with euthyroid controls. The asthmatic patients are much more sensitive than control subjects to bronchoconstrictor effects of PG (36).

There were some suggestions that free radicals might participate in the exacerbation of asthma in some susceptible hyperthyroid patients. Fernandez and Videla (37) reported that liver submitochondrial particles from T₃-treated rats exhibited a remarkable increase in the rate of superoxide radical (O₂⁻) and hydrogen peroxide (H₂O₂) generation compared to those of euthyroid rats. Swaroop and Ramasarma (38) found an increase in H₂O₂ generation in T₄-treated rats and noted that hypothyroid conditions, obtained either by treatment with PTU or by thyroidectomy, caused a decrease in H₂O₂ generation. The antioxidant agent, vitamin E, has been known to protect against the lipid peroxidation in hyperthyroid heart and skeletal muscle (39). In hyperthyroid patients, Krishnamurthy et al. (40) found a parallel decrease in serum vitamin E levels. Hypothyroidism has been known to protect against the free radical damage in ischemic acute renal failure (41). Moreover, some clinical evidence suggested an association of reactive oxygen species with the pathophysiology of bronchial asthma and airway hyperresponsiveness. Kanazawa et al. (42) showed that

thyroid hormone directly stimulated the generation of O₂⁻ from neutrophils and alveolar macrophages. Calhoun et al. (43) showed that the release of O₂⁻ from alveolar macrophages is increased in symptomatic asthma. In addition, Postma et al. (44) showed a significant correlation between O₂⁻ generation of polymorphonuclear leukocytes in vitro and the degree of bronchial hyperactivity in vivo, and in nonallergic patients with chronic airway obstruction. In the lung, PTU protected against the oxygen toxicity, a free-radical-mediated process, whereas T₄ exacerbated it (45).

Kanazawa et al. (46) suggested that oxygen metabolites might play a direct or an indirect role in modulation of airway inflammation. They demonstrated that O₂⁻ production was enhanced in asthmatic patients when compared with healthy control subjects; the production of O₂⁻ also increased with progression of disease and with disease duration. The oxygen radicals produced airway constriction and hyperresponsiveness in anesthetized cats (47). The airway smooth muscle contraction (canine lung strips and bovine trachealis strips) from both hyperoxia and H₂O₂ was blocked by prostaglandin synthetase inhibitors (indomethacin and meclofenamate), but it was partially reversed by various oxygen radical scavengers (48). These findings suggest that the hyperoxic contraction in airway smooth muscle was mediated by active oxygen species, perhaps by their effects on prostaglandin metabolism. Furthermore, some experimental studies have indicated that oxygen metabolites can themselves trigger the release and metabolism of arachidonic acid in isolated perfused lungs (49–52). Tate et al. (50) suggested that thromboxane generation might participate in O₂-metabolite-induced vasoconstriction. They found that O₂ metabolites caused an increase in mean pulmonary artery perfusion pressure in isolated perfused lungs. In addition, the O₂ metabolites also caused a 30-fold increase in perfusate levels of thromboxane B₂ when compared with only a twofold increase in 6-keto-PGF₁. Pretreatment with cyclooxygenase inhibitors, either from aspirin or indomethacin, also blocked thromboxane generation and markedly attenuated pressor responses. Seeger et al. (51) indicated that calcium-calmod-

ulin function and thromboxane generation might be involved in pulmonary vasoconstrictive response to H_2O_2 . Moreover, Burghuber et al. (52) demonstrated that 5-lipoxygenase pathways, as well as cyclooxygenase pathways, were activated during H_2O_2 -induced lung injury and that inhibitors of 5-lipoxygenase or leukotriene action effectively prevented lung injury. Therefore, the oxidant-induced eicosanoid formation might be an important mechanism in the pathogenesis of lung disease.

In summary, the present findings suggest that asthma may develop in a susceptible individual with hyperthyroidism and it is possible that the reactive oxygen species may be a contributory factor in exacerbating wheezing in our hyperthyroid patients.

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