

Association of Seasonal Allergic Rhinitis is High in Graves' Disease and Low in Painless Thyroiditis

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Hashimoto's thyroiditis is thought to be a T-helper cell type 1 (T_H1)-dependent disease, but it is not clear whether Graves' disease is T-helper cell type 2 (T_H2)-predominant or not. T_H1 -predominant diseases are infrequently and T_H2 -predominant diseases are frequently associated with allergic diseases. We examined the prevalence of seasonal allergic rhinitis to Japanese cedar pollen, a typical T_H2 -associated disease, in patients with Graves' disease ($n = 126$), painless thyroiditis ($n = 46$) and Hashimoto's thyroiditis ($n = 88$), and compared them to healthy controls ($n = 766$). Gender and age distribution were not different among patient groups and healthy controls, except for the higher age of patients with Hashimoto's thyroiditis. The prevalence of seasonal allergic rhinitis was significantly high in patients with Graves' disease (42.9%, $p < 0.05$) and low in patients with painless thyroiditis (13.0%, $p < 0.01$) but was not different in patients with Hashimoto's thyroiditis (26.1%) compared to that of healthy controls (32.6%). When patients with painless thyroiditis were included in Hashimoto's thyroiditis group, the prevalence of seasonal allergic rhinitis was 21.6% and significantly different from that of healthy controls ($p < 0.05$). These data indicate that Graves' disease is T_H2 predominant and painless thyroiditis is a T_H1 -predominant disease. Our findings suggest that the shift from T_H2 toward T_H1 immunogenesis may be important for achieving earlier remission of Graves' disease.

Introduction

THE BALANCE of T-helper cell type 1 (T_H1) and T-helper cell type 2 (T_H2) immune responses is thought to be important for the clinical expression of autoimmune diseases (1). In general, one organ has one autoimmune disease but there are two autoimmune diseases in the thyroid gland: Graves' disease and Hashimoto's thyroiditis. Graves' thyrotoxicosis is induced by thyroid-stimulating antithyrotropin (TSH) receptor antibodies (2). On the other hand, autoreactive cellular immunity has been considered to be important for induction of thyroid destruction in Hashimoto's thyroiditis (3). During the clinical course of Hashimoto's thyroiditis or autoimmune thyroiditis, the disease is aggravated subacutely and often develops destruction-induced thyrotoxicosis, called painless thyroiditis or silent thyroiditis. Painless thyroiditis has similar histopathology to that of Hashimoto's thyroiditis (4) and is a result of aggravation of Hashimoto's thyroiditis (5). Thus, it has been suggested that painless thyroiditis is a more activated stage of Hashimoto's thyroiditis (6). We found that the serum concentration of interleukin (IL)-5, a T_H2 cytokine, was significantly greater than that of the normal controls in patients with Graves' dis-

ease but not in patients with painless thyroiditis (7). Serum IL-12, a T_H1 -inducing cytokine, was markedly higher in patients with painless thyroiditis, and the serum IL-12/IL-5 ratio was significantly high in patients with painless thyroiditis but not in Graves' disease (6). These data suggest that Graves' disease is associated with T_H2 predominance and painless thyroiditis with T_H1 predominance. As for Hashimoto's thyroiditis, it is widely considered that the disease is T_H1 predominant, however, in Graves' disease T_H2 predominance is not clear at present.

Recent studies have revealed that T_H1 -predominant diseases were infrequently (8,9) and T_H2 predominant diseases were frequently (10–12) associated with allergic diseases. Japanese cedar trees were planted according to forestation policies after the Second World War and now Japanese cedar pollen is heavily disseminated from late February to late April every year, and cedar pollinosis has become a common allergic disease in the general population in Japan. Moreover, we have frequently observed that Graves' thyrotoxicosis developed or relapsed after attacks of allergic rhinitis (13,14). Therefore, we investigated the prevalence of seasonal allergic rhinitis in patients with Graves' disease, painless thy-

roiditis, and Hashimoto's thyroiditis, in order to clarify the relation to T_H1/T_H2 imbalance.

Materials and Methods

We examined 126 patients with Graves' disease, 46 patients with painless thyroiditis, 88 patients with Hashimoto's thyroiditis, and 766 healthy controls. Diagnosis of Graves' disease was made on the basis of clinical findings and laboratory tests showing a high value of serum thyroid hormones, suppressed TSH, positive anti-TSH receptor antibodies, and/or high radioactive iodine uptake (15). Painless thyroiditis was diagnosed by increased serum thyroid hormones for less than 3 months, positive antithyroid microsomal and/or thyroglobulin antibodies, later development of transient hypothyroidism, and/or low radioactive iodine uptake (15). Hashimoto's thyroiditis was diagnosed by positive antithyroid microsomal and/or thyroglobulin antibodies and presence of diffuse goiter either with euthyroid or hypothyroid condition. Patients who had experienced episodes of painless thyroiditis were included in the group of painless thyroiditis and excluded from the group of Hashimoto's thyroiditis in this study. We obtained informed consent from all patients. Healthy controls mainly consisted of healthy medical staff in Osaka University Hospital who responded well to the questionnaire on seasonal allergic rhinitis.

Seasonal allergic rhinitis was defined at diagnosis of thyroid disease by clinical history (during 5 years preceding diagnosis) of annual recurrence of sneezing, rhinorrhea, nasal congestion, and/or eye itching during the time from late February to late April when Japanese cedar pollen is heavily disseminated. Subjects living outside of the Osaka area were excluded, because the prevalence of seasonal allergic rhinitis is influenced by the local environment.

Statistical differences in the prevalence of seasonal allergic rhinitis between patients groups and healthy controls was calculated by the Mann-Whitney *U* test and a *p* value less than 0.05 was considered to be significant.

Results

As expected, the prevalence of seasonal allergic rhinitis to cedar pollen was as high as 32.6% even in healthy controls in Osaka (Table 1). The prevalence was higher at 42.9% in patients with Graves' disease and significantly different from that of healthy controls.

On the contrary, the prevalence was significantly low (13.0%) in patients with painless thyroiditis. In patients with

Hashimoto's thyroiditis it did not reach statistical significance, although the prevalence was lower than that of healthy controls. There was no significant difference in prevalence between the painless thyroiditis and Hashimoto's thyroiditis groups. When patients with painless thyroiditis were included in the Hashimoto's thyroiditis group, the prevalence of seasonal allergic rhinitis was 21.6%, significantly different from that of healthy controls (*p* < 0.05).

Discussion

Disease associations with autoimmune thyroid disease have mainly been investigated for other autoimmune diseases and little is known about the relation between thyroid disease and allergic disorders (16). Readett (17) reported an increased incidence of clinical thyroid disease in patients with atopic eczema, although this association was not confirmed by Raffle and Hall (18). Serafini et al. (19) described an increased incidence of thyroid autoantibodies in patients with allergic asthma and/or rhinitis. Heymann (20) reviewed the previous reports and suggested that there might be the association of chronic urticaria and angioedema with thyroid autoimmunity. Lanigan et al. (21) reported a high prevalence of chronic urticaria in patients with thyroid disease that included Hashimoto's thyroiditis, Graves' disease, toxic multinodular goiter, autoimmune hypothyroidism, and euthyroid multinodular goiter. Chronic urticaria is not only induced by allergic reaction but also other factors. Therefore, it is difficult to evaluate prevalence of allergic chronic urticaria in patients with Hashimoto's thyroiditis or Graves' disease.

It is necessary to clarify the effect of thyroid functional status on allergic rhinitis. In this study, seasonal allergic rhinitis was defined at the diagnosis of thyroid disease by clinical history. Patients with Graves' disease have annual recurrence of cedar pollinosis even when euthyroid during or after antithyroid drug therapy. Patients with painless thyroiditis are found to have transient thyrotoxicosis but occurrence of allergic rhinitis was low. Thus, it seems unlikely that thyroid functional status is related to allergic rhinitis.

Autoimmune reaction in organ-specific autoimmune diseases is locally limited within the target organs. However, these diseases are also influenced by the systemic immunity in the whole body. For example, autoimmune thyroiditis is aggravated after delivery through systemic immune rebound mechanism (22). Allergic rhinitis is localized inflammation in the nose and eyes induced by allergic reaction, but possibly activates systemic T_H2 immune reaction. We previ-

TABLE 1. PREVALENCE OF SEASONAL ALLERGIC RHINITIS IN PATIENTS WITH AUTOIMMUNE THYROID DISEASE

	Number	Age (years)	Male/Female	Seasonal allergic rhinitis	
				Number	%
Graves' disease	126	36.5 ± 13.7	23/103	54	42.9*
Painless thyroiditis	46	37.0 ± 14.0	5/41	6	13.0**
Hashimoto's thyroiditis	88	45.5 ± 14.3**	12/76	23	26.1
Healthy controls	766	34.3 ± 10.9	154/612	250	32.6

Difference from healthy controls at **p* < 0.05 and ***p* < 0.01.

ously observed that Graves' thyrotoxicosis frequently relapsed or was aggravated after attacks of seasonal allergic rhinitis (13,14). We found that the relapse rate was even higher in patients with Graves' disease who had allergic rhinitis than that in patients without allergic rhinitis (13).

Hashimoto's thyroiditis is widely accepted to be a T_H1 -predominant disease. Graves' disease is believed to be T_H2 -predominant condition, but this is yet not well established. If Hashimoto's thyroiditis were T_H1 -predominant and Graves' disease were a T_H2 -predominant disease, association with allergic disease would be fewer in the former and more frequent in the latter.

Seasonal allergic rhinitis to Japanese cedar pollen is very common in Japan (23) and easy to diagnose because the patients have annual symptoms of pollinosis in spring time. As expected, the prevalence of cedar pollen pollinosis was rather high in the Osaka area even in healthy controls. In patients with Graves' disease, its prevalence was even higher. On the contrary, the prevalence was low in patients with painless thyroiditis. These data strongly suggest that Graves' disease is T_H2 -predominant and painless thyroiditis is a T_H1 -predominant disease. Most patients with Hashimoto's thyroiditis or autoimmune thyroiditis are euthyroid and some of them gradually develop hypothyroidism during the long clinical course. When the disease is activate, patients subacutely develop destructive thyrotoxicosis that is painless thyroiditis. More marked T_H1 -predominance in painless thyroiditis is compatible with the low prevalence of seasonal allergic rhinitis. It is speculated that ordinary patients with Hashimoto's thyroiditis may have an equal balance of T_H1 and T_H2 immunogenesis, and when T_H1 immune reaction is more activate, patients show clinical feature of painless thyroiditis.

Among patients with Graves' disease in remission or near remission, one third relapse into Graves' thyrotoxicosis, but one third develop painless thyroiditis after delivery (24,25). This indicates that T_H2 predominance in untreated patients with Graves' disease may gradually convert to T_H1 -predominance and patients thus achieve remission. Therefore, the immunomodulating therapy shifting T_H2 toward T_H1 immunogenicity may be important for achieving earlier remission of Graves' disease.

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