(4) Etiology of Autoimmune Disease

Etiological Analysis and Complication of Hashimoto's Thyroiditis

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As the etiologic factor to induce autoimmune diseases, the abnormality of antigen (abnormal antigen) or the abnormality of antibody-forming system has been focused. By trigger mechanism (inflammation, trauma, virus infection, etc.), the abnormal antigen can be supposed to acquire antigenicity to induce abnormal antibody formation. On the other hand, as the abnormality of antibody forming system, the hereditary constitution (a genetic defect), the mutation of immune competent cells and the prolonged immunization have been postulated.

The present paper describes the hypothesis of general etiology of autoimmune disease through the clinical manifestations and complications of Hashimoto's thyroiditis and through the experimental thyroiditis.

(1) Clinical manifestation and autoantibody of Hashimoto's thyroiditis

Hashimoto's disease has a high familial incidence and often occurs in middle-age women. In Hashimoto's disease, anti-thyroglobulin antibody (TRC-antibody and precipitating antibody) and anti-microsome antibody are found frequently and also the antibody titers are extremely high. However, in other thyroidal diseases (hyperthyroidism, hypothyroidism, thyroid cancer, simple goiter and non-toxic nodular goiter), both antibodies are found less frequently and also antibody titers are very low.

(2) Possible role of denaturated thyroglobulin (TG) to induce Hashimoto's thyroiditis

Hashimoto's thyroiditis is believed to be one kind of autoimmune disease producing the antibody against TG, because TG that is sequestered into thyroid follicle during embryonal period, happens to be released from the thyroid gland after the birth.

Lately, we found the phenomenon of abnormal thyroid hormone (T_4 (thyroxine) and T_3 (triiodothyronine)) binding in the γ -globulin region in the patients of Hashimoto's thyroiditis, that can be explained for the release of denaturated TG from the thyroid gland¹⁾. In this case, a high binding of T_4 and T_3 in the γ -globulin region was observed by paper and cellulose electrophoresis (Fig. 1). By the absorption of patient sera with TG prior to electrophoresis, the binding of thyroid hormone decreased remarkably. Under the continuous treatment of the patient with prednisolone, the binding in the γ -globulin region was diminished gradually in associ-

Fig. 1. Distribution of $L-T_4^{131}$ in the serum. Cellulose acetate electrophoresis in veronal buffer pH 8.6 $\mu=0.06$.

ation with the decrease of thyroidal antibody.

It has been already reported that such abnormal binding of thyroid hormone in the γ -globulin region was observed by Robbins²⁾ (thyroid cancer), Premachandra³⁾, Roitt⁴⁾ and Mertz⁵⁾ (Hashimoto's thyroiditis). Also, the similar findings in the experimental animals have been reported by Premachandra⁶⁾⁷⁾¹²⁾, Singh⁸⁾, McKenzie⁹⁾, Medda¹⁰⁾, Margherita¹¹⁾, Pogoriler¹³⁾, Beall¹⁴⁾ and Chopra¹⁵⁾.

In our clinic, such abnormal binding was observed in 6 patients of Hashimoto's disease.

To examine the casual factor to evoke the phenomenon, the experimental Hashimoto's thyroiditis was produced in rabbits. In 15 experimental rabbits immunized with native TG (untreated TG), such abnormal binding of thyroid hormone in the γ -globulin region was not demonstrated. However, such abnormal binding was observed in all of rabbits immunized against denaturated TG by heat (70°C for 20 min or 70°C for 10 min) and acid- and alkali-treatment with histological changes in the thyroid gland which can resemble be seen in Hashimoto's disease (Table 1).

From these findings, it seems that the antibody formation against thyronine structure that may act as hapten, becomes to be easy by denaturation of TG.

Table 1. Thyroid Hormone Binding Antibody in Immunized Rabbit Against Denaturated Thyroglobulin (TG)

Antigen Human TG	Antibody for TG	
	Precipitation with untreated TG	T_4 & T_3 binding antibodies Immunized rabbits
Untreated	+	$\frac{0}{15}$
70°C 20min	+	$\frac{4}{4}$
Heated 70°C 10min	+	$\frac{4}{4}$
Acid-treated	+	$\frac{2}{2}$
Alkali-treated	+	$\frac{2}{2}$

From these observations, it is also supposed that in some cases of Hashimoto's thyroiditis the release of denaturated TG from the thyroid gland by the trigger mechanism may be very important factor for the etiology of the disease.

As the denaturation of IgG or DNA as the antigen of rheumatoid arthritis or systemic lupus erythematoses has been demonstrated, the similar phenomenon can be proved to be the etiology of some Hashimoto's diseases.

(3) Complications of Hashimoto's thyroiditis and lupoid hepatitis.

The coexistence of Hashimoto's disease and other autoimmune disease has often been seen.

The present paper describes the complicated case of hepato-thyroidal autoimmune disease. The patient had the symptoms of Hashimoto's thyroiditis with a high titer of anti-thyroid antibody (TRC $>10^{24}$, MCF >320) and increased γ -globulin (6.6 g%) at the time when no liver damage was observed. By the electrophoresis using cellulose acetate membrane, the wavy band was seen in the γ -globulin region that was proved as polyclonal by the immunoelectrophoresis. Two years later, the patient became subicteric and revealed enlargement of the liver and the spleen and also palmar erythema. In the laboratory data, LE phenomenon, RA and Coomb's direct were positive. The autoimmune mechanism was supposed as the etiological factor from the histologic changes in the liver and thyroid. Although the Au antigen was negative, the Au antibody was positive in the patient serum during 3 years (Fig. 2).

Generally, in Hashimoto's thyroiditis the complication with various other autoimmune diseases and also many auto-antibodies are found frequently, therefore the specific genetic factor is postulated as the etiology of autoimmune diseases. If one kind of autoimmune disease is continued by the abnormal antigen as etiologic factor, it is also possible to suppose that other immune diseases may be complicated by the prolonged immunization and the long standing sensitization.

Fig. 2

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