GRAVES' DISEASE AND HASHIMOTO'S THYROIDITIS IN MONOZYGOUS TWINS

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ABSTRACT

Monozygous twins and their family were studied. One twin had Graves' disease and the other had Hashimoto's thyroiditis. Their mother had Hashimoto's thyroiditis and their maternal grandmother and maternal great aunt had hyperthyroidism. Thyroid biopsies were obtained in each of the twins and showed changes of Graves' disease and Hashimoto's thyroiditis, respectively. High concentrations of anti-thyroid microsomal and anti-thyroglobulin antibodies were present by competitive protein binding assay, but LATS was absent in the twins and their mother. The occurrence of Graves' disease and Hashimoto's thyroiditis in monozygotic twins supports the concept of a common genetic aetiologic factor in the basic pathogenesis of these two diseases; however, the expression of this factor is variable, acquired, and, at least in part, genetically independent.

Graves' disease and Hashimoto's thyroiditis are diseases of the thyroid generally in different areas of the clinical spectrum of thyroid disease. Occasionally, however, their clinicopathological spectrums overlap with Hashimoto's thyroiditis occurring in association with Graves' disease (Michaelson & Young

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1970; Eversman et al. 1966). Hyperthyroidism may occur in patients with Hashimoto's thyroiditis (Buchanan et al. 1961; Fatourechi et al. 1971). In both diseases, autoimmune abnormalities exist and may be related to their pathogenesis. Lymphocytic infiltration within the thyroid gland is present to a variable degree in Graves' disease and is characteristic of Hashimoto's thyroiditis. Circulating antibodies to thyroid tissue are present in both diseases (Mori & Kriss 1971).

Although each disease has a genetic predisposition, the exact mode of inheritance has not been established. The report of identical twins, one with Graves' disease and the other with Hashimoto's thyroiditis, and their family lends to further observations on the relationship between the two diseases.

**CASE REPORTS**

**Case 1.** – KEP is a 15 year old white female who presented with a goitre in October 1970. She had an increased appetite with a ten-pound weight loss, nervousness, and amenorrhea. On examination she was hyperkinetic and her pulse was 100. The thyroid gland was three-fold enlarged and asymmetric with a bruit over the larger right lobe. The deep tendon reflexes were hyperreactive. The thyroxine-iodine by column was 8.2 μg/100 ml (normal 3–6.5). The 24-hour radioiodine uptake and scan showed a diffuse uptake of 54% (normal 10–30). She was placed on propylthiouracil with subsequent return to the euthyroid state.

**Case 2.** – KMP is the monozygotic twin of KEP (Fig. 1). She presented with a goitre at the same time her sister did and was asymptomatic. The thyroid was one and one-half-fold enlarged and irregular in consistency. The thyroxine-iodine was 3.1 μg/100 ml. A 24-hour radioiodine uptake and scan showed diffuse uptake of 16.5%. She was started on thyroid extract, 180 mg po daily and a repeat radioiodine uptake was 0%.

**Case 3.** – SP, the 41 year old mother of KEP and KMP, had a left hemi-thyroidectomy in 1960 and has since been on thyroid replacement therapy. Review of the slides made of the thyroid gland that was removed showed Hashimoto's thyroiditis and an area of papillary hyperplasia.

**Case 4.** – ME, the 60 year old mother of SP, was operated on 30 years ago for an »over-active thyroid«. Since her thyroidecetomy she has done well without regrowth of thyroid tissue and is on thyroid extract, 180 mg po daily. The pathology report on the thyroid tissue removed indicated the presence of diffuse hyperplasia.

**Case 5.** – DP, the 18 year old brother of the twins, has been healthy all his life. His thyroid is normal in size and consistency.

The twins have another brother and a father who are living and healthy without history of thyroid disease. ME has a sister who was treated with RAI for hyperthyroidism six years ago.

**METHODS**

Blood was obtained from the twins for serum typing of red cell antigens to confirm the impression of monozygosity of the twins. Serum was obtained from all the cases
for assay of long-acting thyroid stimulator (LATS), anti-thyroglobulin (anti-TG), and anti-microsomal (anti-M) antibodies. LATS assay was performed by bioassay of unconcentrated sera (Kriss et al. 1964). Anti-TG and anti-M assays were performed by competitive binding radioassay (Mori et al. 1970).

Needle biopsies of the thyroid gland were obtained from the twins without difficulty. The tissue cores were fixed in Bouin’s solution, processed routinely, sectioned at 5 μm and stained with haematoxylin and eosin. After the initial sections were reviewed, each biopsy was serially sectioned.

RESULTS

The red cells of each twin typed identically with twenty-one antisera. Both are type O rr (cde/cde), Fy(+/a+b+), Le(a+b–), MNSs, Jka+, K = k+, and P+. In view of identical physical features including hair and eye colour and skin complexion, and identical blood typing, it can be reasonably concluded that the twins are monozygotic.

The results of the thyroid auto-antibody determinations in each case are shown in Table 1. Assay for LATS was negative in each case.

The pathological findings in the biopsies are as follows:

Case 1. – (KEP) The acini varied in size and many showed typical features of hyperplasia, i.e., columnar epithelium, papillary infolding of epithelium and peripheral vacuolization of colloid (Fig. 2). Interstitial aggregates of lymphocytes and a few plasma cells were present, but well defined lymphoid follicles with germinal centres were not seen. A very small amount of fibrous tissue was present.

Case 2. – (KMP) Most of the follicles were small and in many colloid was absent. Lymphoid follicles with germinal centres were the most striking
Fig. 2.
Hyperplastic epithelium in thyroid of KEP. Lymphocytic infiltrate in upper right. (Haematoxylin and eosin stain × 140).

Fig. 3.
KPM. Small follicles with oxyphilic epithelium, and lymphocytic and plasmacytic infiltrates. Lymphoid follicle in upper left. (Haematoxylin and eosin stain × 170).
Table 1.
Serum anti-thyroid-microsomal and anti-thyroglobulin levels in twins and family members studied.

<table>
<thead>
<tr>
<th>Patient</th>
<th>Age</th>
<th>Anti-M (0-10)*</th>
<th>Anti-TG (0-30)*</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. KEK Graves'</td>
<td>15</td>
<td>5000</td>
<td>400</td>
<td></td>
</tr>
<tr>
<td>2. KMP Hashimoto's</td>
<td>15</td>
<td>5000</td>
<td>116</td>
<td>hemi-thyroidectomy 12 years ago</td>
</tr>
<tr>
<td>3. SP Hashimoto's</td>
<td>41</td>
<td>5000</td>
<td>1500</td>
<td>thyroidectomy 30 years ago</td>
</tr>
<tr>
<td>4. ME Graves'</td>
<td>60</td>
<td>330</td>
<td>20</td>
<td></td>
</tr>
<tr>
<td>5. DP Normal</td>
<td>18</td>
<td>160</td>
<td>20</td>
<td></td>
</tr>
</tbody>
</table>

* Indicates normal levels in U/ml.

feature. The parenchyma adjacent to the follicles was infiltrated by lymphocytes and plasma cells, and in these areas, oxyphilic epithelium was present (Fig. 3). Thus, the histological changes were typical of Hashimoto's thyroiditis.

**DISCUSSION**

Despite the differences in the usual clinical presentation of Graves' disease and Hashimoto's thyroiditis, several lines of evidence suggest that the two diseases are closely related and, in fact, may be different manifestations of a common factor.

The clinicopathological spectrums of Hashimoto's thyroiditis and Graves' disease may at times have considerable overlap. Hashimoto's thyroiditis has been reported in euthyroid and hyperthyroid patients with Graves' ophthalmopathy and/or pretibial myxoedema (Michaelson & Young 1970; Eversman et al. 1966). Hyperthyroidism may occur coincident with the findings of mild to severe histological changes of autoimmune thyroiditis (Buchanan et al. 1961; Fatourechi et al. 1971).

Further support for a common factor causing both diseases comes from experimental models. Immunization of rabbits with concentrated homogenate of human thyroid results in the production of a thyroid stimulating anti-thyroid antibody which may increase RAI uptake in the immunized animal (McKenzie 1968; Beall & Solomon 1968). Also, immunization of rabbits with aqueous preparation of heterologous thyroglobulin results in the production of thyroglobulin antibodies and thyroiditis (Weigle & Nakamura 1967). The
production of a thyroid stimulator and cytotoxic antibodies by immunization with thyroid tissue suggests that Graves' disease and Hashimoto's thyroiditis may represent different manifestations of a common autoimmune disturbance.

A clinical correlate to the experimental production of autoimmune thyroid disease is the finding of both thyroid cytotoxic and stimulator autoantibodies in patients with either Hashimoto's thyroiditis or Graves' disease. Anti-M, anti-TG and LATs may be present in the serum of patients with either disease. Mori & Kriss (1971), using sensitive competitive binding radioimmunoassays, found the frequency of abnormal levels of anti-M and anti-TG antibodies in untreated Graves' disease to be 98% and 89% respectively. However, an aetiologic role for any of these antibodies in producing a specific thyroid disease in man has not been established despite this suggestion in experimental animal models.

The genetic relationship between the two diseases also supports the concept of a common pathogenetic mechanism. Hyperthyroidism has been reported to have a high familial incidence (Bartels 1941) and to occur in identical (Hassan et al. 1966) and non-identical twins (Volpé et al. 1970) Hashimoto's thyroiditis also has a high familial incidence (Parisier et al. 1971; DeGroot et al. 1962) and may occur in identical twins (Irvin et al. 1961). Jayson et al. (1967) reported the occurrence of hyperthyroidism in one identical twin whose sister had a goitre, was euthyroid, and thought to have Hashimoto's thyroiditis, although not proven by biopsy.

Several points pertinent to the pathogenetic mechanisms involved in Graves' disease and Hashimoto's thyroiditis can be made from the study of this family. Despite the same genetic constitution, KEP had Graves' disease and KMP had Hashimoto's thyroiditis. The occurrence of these two diseases in their "pure" forms, both clinically and histologically, in identical twins suggests a common basic aetiological factor. The clinical and/or histological expression of this genetic factor appears, at least in part, to be acquired and genetically independent.

It is also of interest that their mother had Hashimoto's thyroiditis and maternal grandmother had hyperthyroidism. The occurrence of both diseases among three generations favours a dominant mode of inheritance for a basic genetic factor causing both diseases.

Examination of serum antibody levels in the twins and other members of their family did not reveal any distinct difference in the nature or quantity of antibodies. Both twins had very high levels of anti-M and the twin with Hashimoto's thyroiditis had lower levels of anti-TG while her mother with Hashimoto's thyroiditis had the highest levels of anti-TG. All the members of the family studied had negative LATS assays. Thus, an aetiological relationship between a specific antibody and either hyperthyroidism or Hashimoto's thyroiditis was not apparent in the twins or their family.
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REFERENCES

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