Clinical and pathological significance of sibling Graves’ disease

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Abstract. The clinical picture and serum antithyroid antibodies in 16 pairs of siblings with Graves’ disease were compared with an age and sex matched group of 32 patients with Graves’ disease who did not have a family history of any thyroid disease (control patients). There was a significant difference in frequency and mean titres of antibodies to thyroglobulin between sibling patients, (positive 76.0%) and control patients (positive 40.0%), but not in microsomal antibodies (sibling; positive 92.0%, control; 92.0%). There were no significant differences in the mean values of 24 h 131I-thyroidal uptake, serum T3U, serum T4 and T3 concentrations before treatment between the two groups. Lymphoid follicles and degeneration of the epithelia were more often found in the thyroid glands of sibling patients than in those of the control patients, when 32 (16 sibling, 16 control) thyroid glands from the same groups in the clinical study, including antibody series, were examined pathologically after subtotal thyroidectomy for Graves’ disease. Moreover, there was a strong tendency to increased lymphocyte and plasma cell infiltration in the thyroid glands of sibling patients with Graves’ disease.

The findings might indicate that Graves’ disease is closely related to Hashimoto’s thyroiditis, especially in sibling patients with Graves’ disease.

Clinical and immunological studies convincingly demonstrate a familial pre-disposition to Graves’ disease (Evans et al. 1967). Although the HLA associations and twin studies clearly indicate that genetic factors are pathogenetically involved, Graves’ disease does not appear to be due to a single gene with a predominant effect, but instead seems to result from a combination of several genetic and environmental determinations (Friedman & Fialkow 1978).

On the other hand, it has been reported that Graves’ disease can occur in patients with normal or even decreased thyroid function though it seems likely that Graves’ disease is a single entity (Solomon et al. 1977; Christy & Morse 1977), and these patients may have variable degrees of autoimmune thyroid destruction thus preventing the expression of their Graves’ hyperthyroidism.

In the present study, we have examined the clinical picture and serum antithyroid antibodies in patients of sibling Graves’ diseases in comparison with the findings from patients with sporadic Graves’ disease without a family history of any thyroid diseases. Moreover, the thyroid glands obtained at subtotal thyroidectomy were examined morphologically to elucidate the difference between Graves’ disease and sporadic Graves’ disease.

Materials and Methods

Subjects
Sixteen pairs of siblings with Graves’ disease were compared to a control group of 32 patients with Graves’
disease (matched for age and sex) with no family history of any thyroid diseases within the second degree relationship. The control group was chosen at random by using the table of random digits from the big stock of patients' data in Kuma Hospital. All had a case history, physical examination and blood chemistry fulfilling the criteria of Graves' disease. Mean (± SEM) values of age of the group of sibling Graves' disease and the control group were 30.7 ± 3.3 and 31.9 ± 2.1, respectively. The sex ratio was 2.6 for women to 1 for men and 2.6, respectively, there is thus no difference between the two study groups in age and sex incidence.

Thyroid sections from subtotal thyroidectomies for Graves' disease from the above mentioned patients in this study were divided in sibling and non-sibling groups and reviewed. Eight pairs of siblings with Graves' disease from the aforementioned 16 pairs of siblings and a group of 16 patients (matched for age and sex) from the control group of 32 patients with Graves' disease who had no family history of any thyroid diseases comprised this histological study. Mean (± SEM) values of ages and sex ratios of women to men were 31.2 ± 2.8, 27.7 ± 0.8, 1.2 and 1.2, respectively, and there was no difference between the two study groups in age and sex ratio.

Moreover, there was no significant differences in relation to the nature of antithyroid drugs and duration of medication as pre-operative preparation between the two groups. Patients with overt autoimmune diseases of other organ systems were excluded from this study.

Serum T₄, T₃ and T₃-uptake (T₃U)

Laboratory determinations of thyroidal status before treatment were performed by measuring serum T₃U with Triosorb kits and serum T₃ and T₄ with RIA kits of Abbott Laboratories (North Chicago). Normal ranges for serum concentrations of T₄ and T₃ in these methods are 5.0–13.8 μg/100 ml and 80–180 ng/100 ml, respectively, and 22–38% for T₃U.

**Determination of thyroidal antibodies**

Thyroidal antibodies to thyroglobulin and thyroidal microsomes were measured before treatment by the tanned red cell haemagglutination technique, using commercially available kits (thyroid test and microsome test, respectively, from Fujizoki Pharmaceutical Co., Ltd., Tokyo, Amino et al. 1976). Because thyroidal antibodies of 7 sibling patients were not detected before treatment, we present data about thyroidal antibodies from 25 patients from each group.

**Pathological examination**

The thyroid glands were removed during the course of subtotal thyroidectomy for Graves' disease. Sections for histological studies were routinely stained with haematoxylin and eosin.

In order to avoid subjective bias, we performed pathological and clinical examinations independently, and compared the findings later. All of the slides were examined by an experienced pathologist without knowing the patient category, and he evaluated the degree of lesion intensity as no lesions (0), focal slight (1.0), focal moderate (2.0) and diffuse moderate (3.0), with regard to lymphoid follicles, infiltration of lymphocytes or plasma cells, small follicles, inequality in size of follicles, volume of colloid, papillary infoldings of the follicular cells with hyperplasia, degeneration of the epithelium, oxyphilia, tall columnar follicular cells and low cuboidal epithelia. Student's t-test was used for statistical analysis of pathological lesion intensity, titres of thyroidal antibodies and for other clinical data between the sibling group and control group.

**Results**

The mean values (± SEM) of age, serum T₄ and T₃ concentrations, T₃U, 24 h ¹³¹I-thyroidal uptake in

<table>
<thead>
<tr>
<th>Group</th>
<th>Age</th>
<th>Sex</th>
<th>T₄ (μg/100 ml)</th>
<th>T₃ (ng/100 ml)</th>
<th>T₃U (%)</th>
<th>¹³¹I-uptake (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibling</td>
<td>30.7 ± 3.3</td>
<td>m = 9, f = 23</td>
<td>20.9 ± 1.4</td>
<td>592 ± 104</td>
<td>46.8 ± 2.2</td>
<td>63.9 ± 3.2</td>
</tr>
<tr>
<td>'Control'</td>
<td>31.9 ± 2.1</td>
<td>m = 9, f = 23</td>
<td>22.4 ± 1.0</td>
<td>434 ± 138</td>
<td>48.2 ± 1.8</td>
<td>59.3 ± 1.6</td>
</tr>
</tbody>
</table>

* Examined numbers of each group. m = male, f = female. All results are mean ± SEM.
sibling Graves' disease, and a control group with Graves' disease (matched for sex and age) are shown in Table 1. There was no significant difference in the mean values of 24 h ¹³¹I-thyroidal uptake, serum T₃U, serum T₄ and T₃ concentrations between the two groups. Moreover, there was no significant difference in the prevalence of post-operative hypothyroidism, spontaneous hypothyroidism, remission hyperthyroidism and eye signs. Only one patient of the control group relapsed into hyperthyroidism. When the goitre size was examined during surgical operation, the weight of the thyroid glands were 43.3 ± 2.5 g (sibling, n = 16) and 50.3 ± 5.6 g (control, n = 16), and significant difference was not observed between the two groups.

The frequency of elevated thyroglobulin and microsomal antibodies of the two groups is presented in Table 2. Antibodies to thyroglobulin were positive in 76.0% of sibling Graves' disease and 40.0% of 'control' patients; the difference was statistically significant at P < 0.01. Microsomal antibodies were positive in 92.0% of sibling Graves' disease and 92.0% of 'control' patients. The frequency of thyroidal antibodies in control patients were similar to the data of Amino et al. (1976). The individual titres of antithyroidal antibodies in 25 patients of each group is shown in Fig. 1. There was also a significant difference in the mean titres of thyroglobulin antibody (P < 0.01) but not in microsomal antibody between the two groups.

Mean (± SEM) values of the intensity of the lesions in the thyroid glands of the two groups (in relation to the 11 components of the pathological lesions) are shown in Fig. 2. There are statistically significant differences between the two groups in lymphoid follicles and degeneration of the epithelium. Moreover, there is a strong tendency to increased lymphocyte and plasma infiltration in the thyroid glands of sibling Graves' disease, but not statistically significant. In addition, significant differences were also found in intensity of oxyphilia of the follicular cells between the two groups. On the other hand, low cuboidal epithelia were found more often in sibling Graves' disease than in 'control' patients, although this was not significant.

Table 2.
Frequency of occurrence of thyroglobulin and microsomal antibodies in sibling patients with Graves' disease and 'Control' patients with Graves' disease without family history of any thyroid diseases.

<table>
<thead>
<tr>
<th>Group</th>
<th>N</th>
<th>TGHA*</th>
<th>MCHA**</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sibling</td>
<td>25 (m = 6, f = 19)</td>
<td>3.3 ± 0.5 (76.0%: m = 7, f = 12)</td>
<td>4.9 ± 0.5 (92.0%: m = 8, f = 15)</td>
</tr>
<tr>
<td>'Control'</td>
<td>25 (m = 6, f = 19)</td>
<td>1.5 ± 0.4 (40.0%: m = 5, f = 5)</td>
<td>6.1 ± 0.5 (92.0%: m = 7, f = 16)</td>
</tr>
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</table>

* Antithyroglobulin haemagglutination antibodies.
** Antithyroid microsomal haemagglutination antibodies.

m = male. f = female. All results are mean ± SEM.
Pathological lesion intensities in the thyroid glands of sibling patients with Graves' disease, and in 'control' patients with Graves' disease without family history of any thyroid diseases.

Discussion

The results of this study clearly show that antibodies to thyroglobulin prior to therapy and morphological changes of the thyroid gland in sibling Graves' disease tend to be similar to findings in Hashimoto's thyroiditis, and are thus more marked in magnitude when compared with sporadic Graves' disease without family history of any thyroid disease. The secondary effect of antithyroid agents on morphological changes is excluded because the type of drug and duration of medication were matched, thus these morphological similarities to chronic lymphocytic thyroiditis might be considered to result from the degree of hereditary involvement. It certainly has been reported that Graves' disease seems more often in families with a history of the disease (Fatourechi et al. 1971).

On the other hand, it seems increasingly evident that Graves' disease is closely related to Hashimoto's thyroiditis, both genetically and pathogenetically, and that each is caused by closely related primary immunological disorders (Volpé et al. 1974; Volpé 1976, 1977). It has been demonstrated that both Graves' and Hashimoto's diseases aggregate in specific families, and thus appear to be genetically induced. Indeed, these two disorders tend to occur in the same families, and may even co-exist within the same thyroid gland. Moreover, several homozygous twins have been recorded where one twin has Graves' disease and the other has Hashimoto's thyroiditis (Volpé et al. 1974).

Moreover, observations that Graves' disease has a wide spectrum of clinical expression have been accumulating (Solomon et al. 1977; Christy & Morse 1977; Cooper et al. 1978). Indeed some patients with reported histological evidence of Hashimoto's disease can present with classical manifestations of Graves' disease (Fatourechi et al. 1971; Hamilton & Maloof 1973). Our sibling patients actually had high thyroidal $^{131}$I-uptakes and were similar to Graves' disease in clinical manifestations except for the high incidence and titres of thyroglobulin antibodies, and the marked similarity to Hashimoto's thyroiditis in histological examination of the excised thyroid glands.

Although it seems that the occurrence of both Graves' disease and Hashimoto's disease in the same patient over time represents something more than a coincidence; common immunological or aetiological abnormalities in both entities remain unclear.

Our studies, indicating high titres of thyroglo-
bulin antibody and similarity of thyroid pathological changes to Hashimoto's thyroiditis in sibling patients with Graves' disease, suggested that these findings might be related to hereditary aetiological factors. It is probable that more detailed immunological studies, including HLA disease associations which we have not done in this study, may permit the identification of subgroups of Graves' disease on the basis of immunogenetics (Solomon et al. 1977).

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References


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