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Clinical Characteristics of Familial Graves' Disease at the Tokyo Women's Medical University Hospital: Higher Male-to-Female Ratio and Earlier Onset Compared to Non-familial Cases

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To characterize the influence of genetic factors on clinical features of Graves' disease (GD), we investigated 28 patients with familial GD, which were patients who had at least one family member with GD within the proband's first-degree relatives. We compared 43 non-familial cases of GD that were selected randomly from patients referred to the Endocrine Clinic of our hospital. The male-to-female ratio was significantly higher in familial than non-familial GD. The age of onset of the disease was significantly lower in familial GD, but we could not detect any statistically significant differences in thyroid hormone concentrations or the levels of thyrotropin receptor-related antibodies. These data suggest that the influences of chromosome X-linked genes or estrogen products may be less important than susceptibility genes for the onset of familial than non-familial GD, and non-genetic factors may have a stronger influence in older patients. The results also suggested that genetic factors may not influence the disease activities by themselves, but further studies are necessary to clarify these issues.

Key words: Graves' disease, familial clustering, clinical characteristics

Introduction

Familial diposition has been reported for autoimmune thyroid diseases including Graves' disease (GD)[1]. Although environmental and hormonal factors are thought to play a role, genetic factors may be the most important trigger for the onset or development of this disease[2]. Recent large twin studies revealed that the concordance of GD in monozygotic twins was 35%, whereas in dizygotic twins, it was estimated to be 3%[3)4)]. In addition, the studies also suggested that genetic factors may account for up to 79% of the predisposition for GD[3)4)]. The genetic factors, however, may be complex, and several different genes may interact to cause GD. Recent investigations on the genes causing susceptibility to GD suggested at least five possible loci, including the genes for major histocompatibility complex on 6p2, cytotoxic T lymphocyte antigen-4 on 2q33, thyroid-stimulating hormone (TSH) receptor on 14q31, and SAS-ZFAT on 5q31-33q[5)-9)].

In addition to these genetic studies, more detailed clinical information is needed on the patients with strong genetic disposition to GD to clarify the genetic and environmental effects on the pathogenic process. As for familial patients, a previous nationwide survey didn't reveal a significant difference between familial and non-familial GD with respect to age, gender distribution, or laboratory findings[10]. However, correct diagnosis of GD and accurate information about family members are difficult to obtain, so we reevaluated the clinical characteristics of clear cases of familial GD.

Subjects and Methods

Subjects

Twenty-eight patients (12 male, 16 female) with familial GD were enrolled in the study. A patient was defined as having familial GD if there was at least one family member with GD within the proband's first-degree relatives as defined by the previous nationwide survey[10]. The diagnosis of GD was confirmed by laboratory findings including elevation of serum free thyroxine (T4) and/or free triiodothyronine (T3), suppression of serum TSH, and the presence of TSH binding inhibitory immunoglobulin (TBII). In some cases, radioactive iodine or thyroidal uptake of $^{99m}TcO_4^-$ was performed to make a definite diagnosis. For the control group, we randomly selected 43 GD patients (8 male, 35 female) that did not have family members or relatives with GD or Hashimoto's thyroiditis. These control patients were referred to the Endocrine Clinic of Tokyo Women's Medical University Hospital in 2000 and were followed by the clinic.

Measurements

Commercial radioimmunoassay kits were used for measurements of free T_3 and free T_4 (Ortho Clinical Diagnostics Co., Tokyo, Japan) and of TSH binding inhibitory immunoglobulin (Cosmic Corporation, Tokyo, Japan).

Statistical analysis

Differences between the male-to-female ratios between the two groups were analyzed by Fisher's exact test where appropriate. All data are expressed as the means ± SD except where indicated. Significance ($p<0.05$) between the measured values was determined by one-way ANOVA where appropriate. Statistical calculations were made using Statview 5.0 (SAS Institute Inc, Cary, NC, USA).

Results

Although we examined only 28 familial patients (12 male and 16 female) and 43 non-familial patients (8 male and 35 female), the difference between the proportion of males (12 of 28 vs 8 of 43, respectively) was significant ($p=0.0334$ by Fisher's exact test).

As shown in the Figure, the age of the onset of disease in male and female patients did not differ

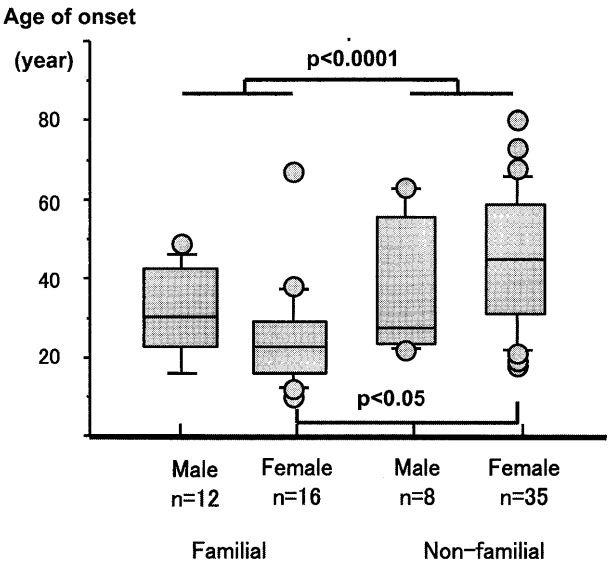

Figure The age of onset of Graves' disease
In familial patients the age of onset was significantly earlier than in patients with non-familial GD ($p < 0.0001$). In female patients, the onset of disease was significantly earlier in familial than in non-familial patients ($p < 0.05$).

(34.1 ± 14.3 vs 38.2 ± 17.9 yr, respectively) but the age of onset in familial patients was significantly earlier than in patients with non-familial GD (27.9 ± 13.0 vs 43.0 ± 16.7 yr, $p<0.0001$). Moreover, for female patients, the onset of disease was significantly earlier in familial than in non-familial patients (24.8 ± 13.5 vs 44.3 ± 16.4 yr, $p<0.05$).

Next we compared free T_3, free T_4, and TBII just before the initial treatment. The number of determinations for these markers was different than the number of patients because some of the patients were referred to our clinic only after the initial treatment and were therefore not included. Free T_4 concentrations in patients with familial and non-familial GD patients were 5.68 ± 2.33 ($n=11$) and 5.28 ± 2.95 ($n=37$) ng/dl, respectively. Free T_3 concentrations in these patients were 15.31 ± 5.19 ($n=11$) and 12.26 ± 6.32 pg/ml ($n=37$), respectively. The levels of TBII in these patients was 39.67 ± 26.56% ($n=28$) and 35.36 ± 24.99% ($n=40$). As shown in the Table, these values were not significantly different between the patients with familial and non-familial GD.

Discussion

According to a previous nationwide survey in Ja-

Table Free T_3, Free T_4 and TSH binding immunoglobulin in familial and non-familial GD prior to the initial treatment

	Familial	Non-familial	p value
Free T4 (n/dl)	5.68 ± 2.33 (n = 11)	5.28 ± 2.95 (n = 37)	NS
Free T3 (pg/ml)	15.31 ± 5.19 (n = 10)	12.26 ± 6.32 (n = 37)	NS
TBII (%)	39.67 ± 26.56 (n = 28)	35.36 ± 24.99 (n = 40)	NS

Data are means ± SD, and the number of patients (n) for each category is shown in parentheses. NS: not significance.

pan, the prevalence of familial GD is 2.1-3.1% of hyperthyroidism, and the relative risk for GD in family members of patients with GD compared to non-family members was estimated to be 19-42[10]. The higher relative risk in familial members suggests genetic influences. In addition, the fact that both GD and Hashimoto thyroiditis are frequently found in members of the same family suggests that they share a genetic predisposition[5)11)]. A genetic predisposition to developing GD is also suggested by the fact that the disease is often associated with other autoimmune disorders including Type 1 diabetes mellitus and systemic lupus erythematosus[5)11)].

In contrast to the previous nationwide study, we found that the proportion of males is significantly higher in familial GD and that the onset of the disease is significantly earlier in familial patients than in non-familial patients. The reason for these discrepancies, may be the differences in the diagnoses as well as the information about the family members. It is generally believed that the correct diagnosis of Graves' disease is sometimes difficult without radioactive iodine uptake even about patients positive for TBII. However, only 41% patients were positive for TBII in the previous nationwide survey. Moreover, the control patients were estimated from the survey of the Ministry of Health, Labor and Welfare of Japan about the patients with thyrotoxicosis who visited outpatient clinic in October 1999. In this study we enrolled patients with definite Graves' disease. The number of the patients is limited but we did not include painless thyroiditis which is more female dominant.

In non-familial patients, the proportion of males was 18.6% (8 out of 43) and the 95% confidence intervals were estimated to be 7.0% to 30.2%. Similarly, the reported proportion of males in the nationwide study was 24.1%[10]. In support of our data, very similar observations were reported in patients who were surgically treated for GD at Noguchi Hospital in Beppu, Japan[12]. The higher male ratio in familial GD suggests that influences of chromosome X-linked genes or effects of estrogen on susceptibility are less prominent on the onset of familial GD. In addition to influences of chromosome X-related genes or estrogen, some reports have revealed gender-specific susceptibility to autoimmune thyroid disease[13)14)]; however, we do not have genetic marker data for these patients, and we had only two patients whose fathers had GD. Therefore, this issue remains to be resolved in future studies.

The difference in the onset of the disease may also be due to the fact that familial GD patients may be more aware of the early signs and symptoms of GD, prompting an earlier examination and diagnosis. Onset of Graves disease is relative sudden and requires medical attention. Therefore, it is highly unlikely that the intergeneration difference in age at onset, which averaged 15.1 yr, is solely a reflection of increased disease awareness. Our observation of an earlier onset of GD in familial cases suggests that the influence of genetic factors is more prominent in younger patients and that environmental factors are more important in late-onset patients. The agrees with the idea that abnormal antigen presentation is more likely to occur in patients with a strong genetic background for GD and in older individuals who have higher chances for exposure to environmental factor such as viral infections.

The early onset of GD in familial cases may be also accounted by the phenomenon termed "genetic anticipation". In numbers of diseases affected by genetic factors, the onset of disease is earlier in each

subsequent generation. Actually genetic anticipation is reported in familial cases of GD[15]. The same tendency was also observed our patients, but the number of pair is too small to estimate statistical significance. As 4 patients of familial cases in our study are the second generation without the first generation, therefore the early onset of the disease in the familial cases may be influenced by genetic anticipation of Graves' disease.

Recent studies on polymorphisms in the gene for cytotoxic T lymphocyte antigen-4, suggest that genetic factors are important for the response of GD to antithyroid drug treatment[16]. The report also suggests that the disease activity itself may be affected by a genetic factor. We therefore compared the patients' thyroid hormone concentrations and the levels of TBII prior to treatment. We did not find a difference in the thyroid hormone concentrations or presence of TSH receptor antibody between the familial and non-familial GD patients. This suggests that the initial thyroid hormone concentrations or presence of TSH receptor-related antibodies may be affected by multiple factors in addition to genetic factors. Such non-genetic factors may include iodine intake, gender, and coexisting destructive thyroiditis.

In conclusion, familial GD has an earlier onset and affects a higher proportion of males than non-familial GD. Therefore, the two forms of GD may be different clinical entities. However, the exact mechanism of the differences remains to be determined.

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家族性バセドウ病の臨床的特徴—東京女子医科大学病院での検討—

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バセドウ病を含む自己免疫性甲状腺疾患には家族集積が認められ，遺伝性因子がその発症や進展に関与している可能性が示唆されている．今回当院に通院中の家族性バセドウ病患者と家族歴のない患者とを比較し，家族性バセドウ病の特徴について臨床的検討を行った．対象は，当院に受診中のバセドウ病患者で兄弟姉妹，親，子にバセドウ病を発症していることが確認された28名を家族性バセドウ病とした．また，2000年に当科初診のバセドウ病患者のうち家族歴を有しないものより43名を受診日より無作為に抽出してコントロールとした．男性の割合は家族性で有意に高く，発症年齢は家族性で有意に低かった．発症時の遊離甲状腺ホルモン，甲状腺受容体抗体は有意差を認めなかった．今回の検討では，若年発症者は遺伝性因子の関与が強く，高齢発症者では環境因子の関与も大きい可能性が示唆された．また，疾患の活動性と遺伝性因子が直接関与しない可能性が示唆された．