Seasonal Variation in Relapse Rate of Graves’ Disease after Thionamide Drug Treatment

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Abstract. Objective: Controversy abounds on the issue of seasonal variation in new onset of Graves’ disease, partly due to the difficulty of precisely dating the exact start of symptoms. To address the possible relationship between climatic changes and disease activity from a different perspective, we reviewed time of relapse during regular follow-up after successful drug treatment with thionamides. Design: Retrospective analysis of a case series in a university clinic. Patients and measurements: We consecutively registered patients who experienced re-emergence of hyperthyroidism between 1992 and 2001 after successful antithyroid drug therapy. Excluded were subjects with superimposing painless thyroiditis, in postpartum, on immunomodulatory drugs, or off thionamides prematurely on their own volition. Results: Fifty-two patients recurred 2 to 36 months after drug cessation. The frequency was higher in spring and summer (March to August) than in autumn and winter (September to February). With a new coated-tube radioreceptor assay, TSH binding inhibitor immunoglobulin activity was detected in sera from 87.5% of the worsened patients. Conclusions: Graves’ disease tends to relapse more frequently in spring and summer. Further clinical studies are warranted to clarify underlying mechanism(s) for this seasonal variation.

Key words: Graves’ disease, Environmental factor, TSH receptor antibodies, Antithyroid drug

 MORE than four decades of research has established the pathogenic role of TSH receptor antibodies for abnormal thyroid stimulation responsible for hyperthyroidism in Graves’ disease [1]. However, the exact causes of disturbed immunoregulation leading to the production of these autoantibodies remain elusive. Indeed, as an autoimmune thyroid disorder, Graves’ disease could well be multifactorial [2]. Environmental factors such as climate and iodine intake may modify phenotypic presentation of the disease, together with ethnic and genetic background, most famously represented by HLA-haplotype [3, 4]. And emotional stress [5, 6] may influence neuro-immunological homoeostasis [7].

There is considerable controversy over seasonal changes in the onset of Graves’ disease. Whereas some authors reported an increased occurrence in the warmer months of the year [8, 9], others failed to find any significant difference between seasons [10, 11]. This discrepancy could be partly due to a bias toward increased awareness of thyrotoxic symptoms on warmer days [8] in addition to the effect of differing amounts of iodine in the diet [9]. In fact, recollecting the exact period of symptomatic onset has often proved difficult for many patients with Graves’ disease, who may have been in mildly hyperthyroid state for months or even years before first presenting themselves to thyroid clinics. To obviate this uncertainty of the time of new onset, we looked into possible seasonal changes in frequency of relapse after antithyroid drug treatment in order to precisely determine when the disease regained its momentum. Moreover, in recent cases, we also measured activity of TSH-receptor antibodies to
see whether the assay could serve as a sign of aggravation.

Patients and Methods

In this retrospective study, we systematically reviewed the medical records of patients with Graves’ disease treated at the Department of Nuclear Medicine, Kyoto University Hospital, and selected all cases that had relapsed during regular follow-up between 1991 and 2001. Pretreatment diagnosis of the disease was confirmed by hyperthyroxinemia, suppressed serum TSH level, and presence of diffuse goiter with substantial homogeneous uptake of technetium pertechnetate. Using these criteria, 511 new cases were registered during the observation period stated above; 136 of them were still on antithyroid drug treatment at the end of year 2001, 108 chose ablative therapy (radioiodine or thyroidectomy), and 61 moved to other clinics or were otherwise lost to follow-up. In 206 patients successfully treated with thionamide anti-thyroid drugs (methimazole in most subjects; propylthiouracil in exceptional ones who showed allergy to the former), the therapy was terminated after at least 6 months of both symptomatic and chemical euthyroid state on minimal maintenance dose of 1 tablet (5 mg of methimazole or 50 mg of propylthiouracil) every other day. Laboratory indices to judge thyroid status included TSH (reference range 0.30–3.90 mU/L) as well as fT4 (0.98–1.77 ng/dl) and T3 (94–154 ng/dl) or free T3 (2.2–4.1 pg/ml). Post-therapy follow-up was done in intervals not exceeding 2 months, usually up to 24 months, but longer in some cases with the patients’ request. Relapse of Graves’ disease was ascertained either by hyperthyroxinemia with re-appearance of overt and persistent (more than 2 months) thyrotoxic symptoms such as palpitation, excessive sweating, finger tremor, easy fatigability and weight loss, or by worsening biochemical thyrotoxicosis at two consecutive visits regardless of symptoms. When necessary, possibility of superimposing painless thyroiditis was ruled out by pertechnetate uptake test [12]. Excluded were cases of postpartum reworsening, subjects who took corticosteroids, interferons, or other potential immunomodulatory agents, and those whose condition worsened after premature discontinuation of thionamides on their own will and against the attending physician’s advice. Nor were patients with previous history of thyroidectomy or radioactive iodine therapy included.

TSH-receptor antibodies were tested as TSH-binding inhibitory immunoglobulins (TBII) activity of serum by two commercial kits for radioreceptor assay according to manufacturers’ instructions. The first one, which has been widely used in clinical practice for two decades, is a precipitation assay with solubilized porcine thyroid TSH-receptor [13, 14]; the second is an improved system that uses test tubes coated with recombinant human TSH receptor [15]. TBII was expressed as % binding inhibition to facilitate comparison of the two systems. From a preliminary evaluation with sera from healthy volunteers and patients with untreated Graves’ disease, cut-off value was set at 10% for both kits.

Results

In the 10-year period, there were 52 episodes of relapse in 38 subjects after 2 to 36 months (median: 14) from the discontinuation of antithyroid drug. The patients were 3 males and 35 females, aged 20–61 (median: 41) at the time of aggravation. Ten had twice and 2 had thrice experienced the re-worsening. In the mean time, 168 formerly treated subjects were free from hyperthyroidism without medication at the end of year 2001. As shown in Fig. 1, there was considerable variation in the months in which relapse occurred. Employing the chi-square test, there was a statistically
SEASONS AND RELAPSE OF GRAVES’ DISEASE

Table 1. Seasonal occurrence of relapse of Graves’ disease after cessation of antithyroid drugs

<table>
<thead>
<tr>
<th>Season</th>
<th>Number of patients</th>
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<tbody>
<tr>
<td>Spring (March to May)</td>
<td>16</td>
</tr>
<tr>
<td>Summer (June to August)</td>
<td>19</td>
</tr>
<tr>
<td>Autumn (September to November)</td>
<td>5</td>
</tr>
<tr>
<td>Winter (December to February)</td>
<td>12</td>
</tr>
<tr>
<td>Total</td>
<td>52</td>
</tr>
</tbody>
</table>

χ² = 8.46, 0.01 < p < 0.05 by chi-square test

Table 2. Positive rate of TSH-receptor antibodies by two radioreceptor assay kits in sera of patients treated with antithyroid drugs

<table>
<thead>
<tr>
<th></th>
<th>Before relapse</th>
<th>At relapse</th>
</tr>
</thead>
<tbody>
<tr>
<td>Precipitation assay</td>
<td>3/9 (33.3%)</td>
<td>20/29 (69.0%)</td>
</tr>
<tr>
<td>Coated tube assay</td>
<td>6/8 (75.0%)</td>
<td>14/16 (87.5%)</td>
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Discussion

We believe that the follow-up schedule mentioned above should have successfully eliminated any bias of symptomatic awareness as planned. A recent report from another institution [16], using similar criteria for cessation of antithyroid drugs, observed a low relapse rate of 19% comparable to ours (18% per patient basis, 25% per case basis). A 6-month period of minimum maintenance dose (after success with regular initiation regimen and tapering) thus seems sufficient to get Graves’ disease well under control in most cases. What then is the cause of the observed vernal and summery increase of relapse? Regarding spring surge, Hidaka et al. previously proposed an intriguing hypothesis that aggravation of Graves’ disease could be triggered by allergic rhinitis [17]. Unfortunately, we could not systematically survey the prevalence of pollen allergy and its potential relationship with the worsening of hyperthyroidism among subjects visiting our thyroid clinic. Nor had we enough hematological data on the patients with relapse to affirm or deny transient eosinophilia, which could reportedly indicate allergic rhinitis preceding aggravation of Graves’ disease [17].

Alternatively, since the Japanese fiscal and academic year begins in April, it seems that more life events occur in spring than in other seasons, such as graduating from school, getting new jobs, parting from family and friends, moving to new locations, getting promotions at work, and so on. Some of these events, even if positive in nature, could cause emotional stress that may precipitate Graves’ disease [6].

It would be very helpful if TBII assays could predict an impending relapse during follow-up. To our regret, however, the coated tube assay was positive throughout the course in some subjects (even before stopping ATD), and was only positive at relapse in some others. Only 2 out of 16 subjects had an ideal fluctuation of TBII values in that assay where the test was positive in just one blood sampling before the re-worsening. We are currently investigating a prospective trial to determine at what threshold we can divide subjects into groups at low and high risk of relapse. It may well be that activity of TSH receptor antibodies alone cannot accurately predict the outcome but it can when combined with other indices such as goiter size and thyroidal uptake [18].

In conclusion, a cohort of patients with Graves’ disease showed an increased frequency of relapse in spring and summer. Analyzing the underlying cause(s) of this seasonal variation in prospective studies with larger population may help to elucidate the pathogenesis of the illness.

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References