Seasonal Recurrence of Transient Hypothyroidism in a Patient with Autoimmune Thyroiditis

MICHIKO YAMAMOTO, NAOHIKO SHIBUYA*, LI CHANG CHEN AND ETSURO OGATA

Fourth Department of Internal Medicine, University of Tokyo School of Medicine, 3-28-6 Mejirodai, Bunkyo-ku, Tokyo 112 and Mitsubishi Yuka Laboratory of Medical Science*, 1-2-10 Narimasu, Itabashi-ku Tokyo 175, Japan

Abstract

Two postpartum and 7 spontaneous episodes of transient hypothyroidism developed during 5 years of observation in a florist with autoimmune thyroiditis and seasonal allergic rhinitis. The spontaneous episodes recurred twice a year regularly in spring and in autumn, the seasons of her allergic rhinitis. In most of these episodes as well as in the postpartum ones, hypothyroidism was preceded by transient thyrotoxicosis. In addition to the similarity in the clinical course, the changes in antimicrosomal antibody titers in pregnancy-unrelated episodes were almost identical to those in postpartum episodes. Throughout the observation periods, she had supranormal serum total immunoglobulin (Ig) E concentrations and high antigen-specific Ig E levels for various pollen extracts such as cedar and ragweed. However, we failed to demonstrate a correlation between thyroid function and total or any antigen-specific Ig E level.

The present findings suggest that the pregnancy-unrelated thyroid dysfunction in our patient developed as a result of silent thyroiditis and through similar immunological mechanisms to those in postpartum thyroiditis. And it is suspected, though unproved, that the seasonal recurrence of pregnancy-unrelated thyroiditis has some causal relation to her allergic disease.
former, termed postpartum thyroiditis, are well delineated by a number of studies (Amino et al., 1976; Ginsberg and Walfish, 1977; Amino et al., 1977). In contrast, concerning pregnancy-unrelated silent thyroiditis, the following questions remain to be answered. Is it a similar disorder to postpartum thyroiditis or a separate one? What etiologic factors and mechanisms are involved in its pathogenesis?

We report here a patient who had 2 episodes of postpartum thyroiditis and 7 episodes of similar spontaneous thyroid dysfunction occurring seasonally. A Five year follow-up study in this patient gave us an opportunity to examine whether there are any differences between postpartum and pregnancy-unrelated thyroid dysfunctions when compared in the same patient. In addition, we attempted to identify possible causes of the pregnancy-unrelated thyroid dysfunctions in this patient.

Methods

Serum samples used in the studies were obtained from the patient at 1-8 week intervals during the observation period and the serum was divided. Half was used for the immediate assessment of her thyroid status and also for routine examinations. The remainder was stored at -20°C for further examinations. Using the stored serum samples, serial measurements of thyroxine (T₄), thyrotropin (TSH), thyroid antimicrosomal antibodies (MsAb), immunoglobulin (Ig) G, total Ig E and antigen-specific Ig E were performed in the same assays.

Serum T₄ and TSH were measured with commercially available RIA kits (T₄ RIA, Dainabot Radioisotope Labs., Tokyo, and TSH Kit, Daiichi Radioisotope Labs., Tokyo). The normal ranges are 5-12 µg/dl and less than 6 µU/ml, respectively. MsAb titers were estimated quantitatively by tanned red cell hemagglutination technique (Microsome Test, Fujirebio Inc., Tokyo, Japan). Ig G, A, and M were measured by the radial immunodiffusion method. Total serum Ig E was measured by radioimmunosorbent test (Phadebas-Ig E-Test, Pharmacia, Uppsala, Sweden). Specific serum antibodies of the Ig E class directed against common inhalant and food antigens were measured by radioallergosorbent test (RAST, Pharmacia, Uppsala, Sweden). The results were presented either as PRU/ml or as grades from [-] to [3+]. The normal range is [-], or less than 0.34 PRU/ml. TSH binding inhibitory immunoglobulin (TBI) was analyzed with a commercial kit (Travenol Co. Ltd., Tokyo). Other measurements were performed by routine laboratory methods.

Case Report

Clinical course

A 29-year-old woman working at a flower shop was first seen in December, 1980 with symptoms suggestive of hypothyroidism. She had been in good health except for suffering from seasonal allergic rhinitis and conjunctivitis in the past few years. No history of drug or food allergy was documented. In October 1980, one month after the delivery of her third child, she experienced typical symptoms of thyrotoxicosis such as palpitation, tremor, excessive sweating and body weight loss (−4 kg/month). In November, when the thyrotoxic symptoms had subsided and body weight recovered, she noticed swelling of the anterior neck. Physical examination at the initial presentation revealed a diffuse non-tender goiter, estimated to weigh 80 g. A diagnosis of postpartum hypothyroidism was made on the basis of history, clinical findings and laboratory data; low serum T₄ (1.7 µg/dl), high serum TSH (81 µU/ml), and positive MsAb titers (1:409600 <). The patient was followed thereafter until her next episode of postpartum hypothyroidism in 1985.

During the four years between the two consecutive episodes of postpartum hypothyroidism, she had 7 episodes of pregnancy-unrelated transient hypothyroidism. In most of these episodes, clinical and biochemical thyrotoxicosis preceded 1-2 months prior to
### Table 1. Clinical and laboratory findings in 9 episodes of transient thyroid dysfunction

<table>
<thead>
<tr>
<th>Episode</th>
<th>Relation to delivery</th>
<th>Duration of symptoms (week)</th>
<th>Severity of symptoms*</th>
<th>Maximal serum $T_4$ (µg/dl)</th>
<th>Duration of symptoms (month)</th>
<th>Minimal serum $T_4$ (µg/dl)</th>
<th>Maximal serum TSH (µU/ml)</th>
<th>[time of measurement]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st</td>
<td>yes</td>
<td>4</td>
<td>++</td>
<td>N.D.</td>
<td>3</td>
<td>0.5</td>
<td>160</td>
<td>Jan. 1981</td>
</tr>
<tr>
<td>2nd</td>
<td>no</td>
<td>1</td>
<td>+</td>
<td>N.D.</td>
<td>1</td>
<td>1.8</td>
<td>67</td>
<td>May 1981</td>
</tr>
<tr>
<td>3rd</td>
<td>no</td>
<td>2</td>
<td>++</td>
<td>8.1</td>
<td>1</td>
<td>1.6</td>
<td>57</td>
<td>Oct. 1981</td>
</tr>
<tr>
<td>4th</td>
<td>no</td>
<td>3</td>
<td>++</td>
<td>12.5§</td>
<td>1.5</td>
<td>1.0</td>
<td>99</td>
<td>Apr. 1982</td>
</tr>
<tr>
<td>5th</td>
<td>no</td>
<td>1</td>
<td>+</td>
<td>9.8</td>
<td>1</td>
<td>2.5</td>
<td>45</td>
<td>Sep. 1982</td>
</tr>
<tr>
<td>6th</td>
<td>no</td>
<td>4</td>
<td>++</td>
<td>18.9</td>
<td>1.5</td>
<td>1.2</td>
<td>116</td>
<td>Sep. 1983</td>
</tr>
<tr>
<td>7th</td>
<td>no</td>
<td>3</td>
<td>+</td>
<td>12.4§</td>
<td>1</td>
<td>2.6</td>
<td>42</td>
<td>Sep. 1983</td>
</tr>
<tr>
<td>8th</td>
<td>no</td>
<td>3</td>
<td>++</td>
<td>13.6</td>
<td>0†</td>
<td>6.5</td>
<td>9</td>
<td>Apr. 1984</td>
</tr>
<tr>
<td>9th</td>
<td>yes</td>
<td>5</td>
<td>++</td>
<td>24.3</td>
<td>2</td>
<td>1.4</td>
<td>72</td>
<td>Jun. 1985</td>
</tr>
</tbody>
</table>

* The numbers of + symbols represent the numbers of thyrotoxic symptoms among palpitation, tremulousness and body weight loss.

N.D.: Not determined.

§ Thyrotoxicosis was confirmed by absence of TSH response to thyrotropin-releasing hormone (500 µg, iv).

† Biochemical hypothyroidism continued for a month.

---

**Fig. 1.** Change in serum TSH levels during 5 years of follow-up. Between two episodes (1st and 9th) of postpartum hypothyroidism, 7 episodes (from 2nd to 8th) of pregnancy-unrelated transient hypothyroidism occurred twice a year with such regularity that the peak TSH values were obtained in spring (March-May) and in autumn (September-October). During pregnancy, however, the episode in spring (8th) was unusually mild and no hypothyroidism developed in autumn.
the onset of hypothyroidism (Table 1). None of the episodes was accompanied by fever or pain in the neck. The goiter size changed almost in parallel with serum TSH concentration, but it did not become normal even in the euthyroid stage. The symptoms of seasonal allergic rhinitis and conjunctivitis appeared in the early spring and in the early autumn every year, apparently concurrent with the development of thyrotoxic symptoms. The allergic symptoms were generally severer in spring than in autumn. Excessive ingestion of iodide or organic iodine before the onset of thyroid dysfunction was denied in reply to careful inquiry. Dietary manipulation of iodine intake (taking iodine-rich seaweed every day for a month after abstaining from taking it for a month), conducted from May to June 1982, had no apparent effect on her thyroid function. During the study period, she did not take any medication except for the period from February to August 1981 when small doses (10–20 μg/day) of triiodothyronine was given as a replacement therapy (Figure 1).

**Laboratory findings**

As shown in Figure 1, pregnancy-unrelated spontaneous episodes of transient hypothyroidism (from 2nd to 8th) recurred twice a year regularly. Though the severity and the duration of hypothyroidism varied among the episodes (Table 1), the highest TSH value and/or the lowest T₄ value in each episode was obtained in spring (March–
May) and in autumn (September-October). Apart from the 8th episode which was observed in early pregnancy and whose severity was exceptionally mild, hypothyroidism was severer in the episodes in spring than those in autumn (Figure 1 and Table 1). Preceding transient thyrotoxicosis was confirmed biochemically in 4 of 7 spontaneous episodes of hypothyroidism (Table 1). In general, thyrotoxicosis was severer in the episodes which occurred in spring than those in autumn (Table 1). Thus, there was a correlation between the severity of preceding thyrotoxicosis and subsequent hypothyroidism. The only exception is the 8th episode, in which the increase in TSH was disproportionately small when compared to the severity of preceded thyrotoxicosis (Table 1). TBII was always negative in both thyrotoxic and hypothyroid stages.

Serial measurement of MsAb titers revealed that there was an overall tendency for the bottom values to decrease between the peaks (Figure 2). However, in each pregnancy-unrelated episode, MsAb titers changed similarly to those in postpartum thyroiditis (Amino et al., 1978a): they increased in the hypothyroid stage and gradually decreased in the recovery stage (Figure 2). Not the peak value itself but the magnitude of increase in MsAb titers in individual episodes had a rough correlation with the corresponding peak TSH value (Figures 1 and 2).

Serum Ig G and total Ig E concentrations were supranormal whenever measured (Figure 2), whereas serum Ig A and Ig M were within the normal range (data not shown). As shown in Figure 2, serum Ig G changed almost in parallel with MsAb titers during the period between the 4th and 6th episodes and also around the 9th episode after delivery. In contrast, we could not find any regularity in the change in the serum total Ig E concentration until she became pregnant. During pregnancy, serum Ig E and Ig G concentrations were relatively stable and their changes were similar to those in normal pregnant women (Amino et al., 1978b). After delivery in the state of postpartum thyrotoxicosis, which was observed in March, Ig E peaked coinciding with her allergic symptoms and then gradually decreased in the hypothyroid stage, when the allergic symptoms had subsided. The change in Ig E concentrations in the postpartum period was opposite to the changes in serum Ig G and MsAb titers.

Semiquantitative determination of antigen-specific Ig E gave positive results ([+ ±] to [3+], or 0.37 to more than 17.5 PRU/ml) for a variety of pollen extract antigens such as cedar, ragweed and grass. Among them, Ig E antibody level for ragweed was always the highest (scale out). The results were negative for other non-seasonal common inhalant allergens such as house dust, animal danders and fungi. Serial tests of the diluted serum samples for the antigen-specific Ig E levels for cedar, the most common allergen for seasonal rhinitis, and ragweed did not demonstrate seasonal regularity in their changes. They fluctuated in the supranormal ranges (higher than 3.8 PRU/ml for cedar and higher than 100 PRU/ml for ragweed) throughout the year. Thus we could not identify the particular antigen-specific Ig E which might have a seasonal association with thyroid dysfunction, nor the most probable antigen(s) responsible for her allergic rhinitis.

Discussion

The patient reported here had 7 episodes of spontaneous hypothyroidism during 5 years of observation between 2 episodes of postpartum hypothyroidism. The diagnosis of silent thyroiditis is strongly suggested in four (4th, 6th, 7th and 8th) episodes of spontaneous hypothyroidism as well as in two postpartum episodes because they were preceded by self-limiting thyrotoxicosis. Although no radioactive-iodine study was per-
formed during thyrotoxic stages in these episodes, it is unlikely that she suffered from high uptake transient thyrotoxicosis (Hashitoxicosis). Very short duration (less than 1 month) of thyrotoxicosis, consequent development of hypothyroidism with elevated TSH levels, and a general correlation between the severity of thyrotoxicosis and of hypothyroidism among episodes appear to be supportive evidence of destruction-induced thyroid dysfunction. Subacute thyroiditis is denied by the absence of tenderness in the thyroid gland and also by laboratory findings of a normal erythrocyte sedimentation rate and negative C-reacting protein (data not shown).

It remains speculative that silent thyroiditis is also a cause of the episodes of spontaneous hypothyroidism (2nd, 3rd and 5th) which were not preceded by biochemically confirmed thyrotoxicosis. However, it should be stressed that in postpartum thyroiditis, an established form of silent thyroiditis, hypothyroidism predominates over thyrotoxicosis occasionally in patients who had high MsAb titers (Jansson et al., 1984). According to an extensive study of Amino and co-workers on the clinical course of postpartum thyroiditis (Amino et al., 1982), the thyrotoxic phase is seemingly absent in 8 of 25 episodes in patients with positive MsAb titers. Thus, by analogy with postpartum thyroiditis, it is probable that pregnancy-unrelated silent thyroiditis also follows a clinical course in which no thyrotoxic phase is recognized.

Previous studies have shown that most of the clinical and histological findings are similar in postpartum and pregnancy-unrelated thyroiditis (Woolf, 1980) but that there are several differences between them such as the goiter size, thyroid autoantibody titers, and recurrence rate (Volpe, 1985). On the other hand, the results of the present study indicate that there are no differences in the changes in goiter size and MsAb titers between postpartum and pregnancy-unrelated episodes, so far as they occur in the same patient. In addition, our study supports the previous observation that, similarly to postpartum thyroiditis (Amino et al., 1977; Dailey, 1979; Fein et al., 1980), pregnancy-unrelated thyroiditis recurs frequently in some patients with autoimmune thyroiditis (Kreider, 1977; Gorman et al., 1978; Grenfell et al., 1980; Taylor and Sheeler, 1982).

What are the mechanisms for recurrent episodes of silent thyroiditis? As for postpartum thyroiditis, it is supposed that the immunological abnormalities which predispose to postpartum thyroiditis are continuously present in patients with previous episodes (Dailey, 1979). If this is the case, pregnancy-unrelated thyroiditis may recur every time the causative mechanisms operates in susceptible patients such as ours, who have high MsAb titers and episodes of postpartum thyroiditis.

Seasonal regularity is an outstanding characteristic of the recurrent episodes of spontaneous thyroid dysfunction in the present case. In this regard, it is noteworthy that several case reports from Japan (Kato et al., 1983; Yamamoto et al., 1984) and other countries (Gorman et al., 1978; Frey, 1981; Riddervold, 1983; Solem and Svaar, 1984) documented rather regular recurrence of transient thyrotoxicosis and/or hypothyroidism. These case reports, along with the present experience, suggest that some seasonal factors are responsible for the exacerbation of autoimmune thyroiditis and the resultant development of destructive thyroiditis. Among the possible etiologic factors which could change seasonally, however, there is no evidence that viral infection preceded each episode in the present case. Likewise, we find no evidence that iodine played a primary role in the development of destructive thyroiditis (Sovoie et al., 1975).

A careful review of the dietary and medical history of our patient excluded the ingestion of much iodine before the onset of
thyroid dysfunction. Furthermore, we confirmed that dietary manipulation of iodine intake in our patient did not induce destructive thyroiditis or prevent its occurrence.

It is of interest that the present case was suffering from allergic rhinitis in the seasons of thyroid dysfunction. Although no causal relationship between allergic diseases and silent thyroiditis has hitherto been suspected, our observation suggests a possible immunological relationship between them rather than a coincidental association. Thus we speculated that allergic rhinitis related antigen-antibody reaction or other associated immunological disturbances had modified the immunoregulatory mechanisms and led to the consequent destructive thyroiditis. However, the laboratory findings in the present study are insufficient to support the above speculation. We could not identify the most probable antigens for her allergic rhinitis because she, working in a flower shop, had Ig E antibodies to almost all pollen antigens. Nor could we demonstrate a correlation between thyroid function and the serum Ig E concentration.

Nevertheless, we think that the present observations may add a useful information to the understanding of the endemic aspects of silent thyroiditis. Assuming that some allergies to certain environmental factors are involved in the pathogenesis of silent thyroiditis, we could better explain the mechanisms involved in yearly change and geographic variation in the frequency of this disease (Vitug and Goldman, 1985). Further study will be necessary to clarify the exact immunological relationship between allergic disease and transient thyroid dysfunction in our patient and also to test whether our speculation on this issue can be applied to other patients with similar disorders.

Acknowledgement

We are grateful to Ms. Akiko Kojima for assistance in preparing the manuscript.

References


