IDENTICAL TWIN SISTERS WITH CLOSE ONSET OF GRAVES' DISEASE AND WITH MULTIPLE HLA SUSCEPTIBILITY ALLELES FOR GRAVES' DISEASE

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Abstract

Context. Autoimmune thyroid disease is considered a multifactorial disorder in which autoimmunity against thyroid antigens is facilitated by exposure to endogenous and environmental factors. We present here a rare case of identical female twins who developed consecutively Graves' disease within a few months and had three HLA susceptibility alleles for the development of Graves' disease.

Subjects. A 28-year-old woman was referred to our hospital complaining of thirst, sweating, palpitations, tremor and skin rash. Laboratory data showed hyperthyroidism with antibodies against the thyroid stimulating hormone receptor and ultrasonography of the thyroid revealed enlargement with hypervascularity. Her identical twin was referred to our hospital because of similar symptoms.

Result. We diagnosed them with Graves' disease and both were treated with methimazole. Human leukocyte antigen genotyping showed that both twins possessed the DRB1*04:05, DQB1*04:01:01, DPB1*05:01 haplotype, which confers susceptibility to Graves' disease.

Conclusions. This case supports the hypothesis that interaction of multiple human leukocyte antigen susceptibility alleles as well as genetic background and environmental factors might synergistically contribute the close timing in Graves' disease onset.

Key words: Idiopathic bilateral adrenal hemorrhage, spontaneous regression.

INTRODUCTION

Autoimmune thyroid disease (AITD), which includes Graves' disease (GD) and Hashimoto's thyroiditis, occurs as the result of an immune response against thyroid antigens (1, 2). It is well known that genetic factors significantly contribute to the pathogenesis of GD (1-3). We report the case of Japanese identical twin sisters (Twin A and Twin B) who developed GD approximately a few months apart and were initially treated with medication.

Human leukocyte antigen (HLA) genotyping was performed and both twins possessed at least three HLA susceptibility alleles for GD.

The number of case reports of identical twins developing GD is small (4-7). In these cases, the interval between the development of GD in the two twins ranged from less than one year (6) to 5 years (7), although the twins shared comparable environmental circumstances and had similar laboratory results, including anti-thyroid antibodies. To the best of our knowledge, there are no case reports of identical twins who developed GD with similar timing of onset and who possessed multiple HLA susceptibility alleles for developing GD. Thus, in addition to environmental factors and antibodies against thyroid gland tissue, we considered that three HLA susceptibility alleles (HLA-DPB1*05:01, DRB1*04:05, and DQB1*04:01) affected the close timing of GD onset.

CASE PRESENTATION

Twin A and Twin B were born in 1985 after an uncomplicated pregnancy. Both have lived in the same city all their lives and may have been exposed to similar environmental risk factors, such as iodine intake, smoking, and infectious agents. They have no previous history of other diseases and were not taking any medications at the time of GD onset.

Twin A is single, with no history of pregnancy. Twin B is married and had two pregnancies, at age 22 and 26, both of which resulted in live births. Twin A and Twin B started smoking cigarettes as teenagers. Their family history is significant for their father being diagnosed with GD 23 years prior to this report; he was treated with subtotal thyroidectomy. The twins' elder sister is euthyroid.

Twin A is a 28-year-old woman. In May 2013, she began experiencing increased thirst and sweats.

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Figure 1. Symptoms of Twin A and Twin B prior to the first visit of Twin A to our department.

Figure 2. Ultrasonography in Twin A (a, b) and Twin B (c, d). These images show diffuse enlargement and hypoechogenicity (a, c) and hypervascularity (b, d) of the thyroid, respectively.

One month later, she noted palpitations and a slight postural tremor in the fingers bilaterally (Fig. 1). In August 2013, she developed a rash and pruritus over the skin of the anterior chest and consulted her family doctor. Based on her clinical presentation she was suspected of having hyperthyroidism, and was referred to our hospital in September.

On physical examination, her pulse was regular at 115 beats per minute (bpm) and 12-lead electrocardiogram (ECG) tracing was normal except for sinus tachycardia. Her eyelids were not edematous. Her skin was warm and moist, with erythema over the anterior chest, which was pruritic. No ophthalmologic findings were appreciated. The entire thyroid gland was symmetrically enlarged, non-tender, smooth, elastic, and firm in consistency.

On laboratory testing, Twin A's serum free triiodothyronine (fT3) was 24.8 pg/mL (normal range, 2.39–4.06 pg/mL) and free thyroxine (fT4) was 9.26 ng/dL (normal range, 0.71–1.52 ng/dL) (Table 1). Thyroid stimulating hormone (TSH) was suppressed to an undetectable level (normal range, 0.51–4.26 μ IU/mL), indicating a thyrotoxic state. Antibodies against thyroid peroxidase (TPO), thyroglobulin (Tg), and TSH receptor (TR) were strongly positive (Table 1). Ultrasonography (USG) of the thyroid revealed diffuse enlargement and moderate diffuse hypoechogenicity (Fig. 2a). Color Doppler USG showed moderate hypervascularity (Fig. 2b).

Twin A was initially treated with 15 mg of methimazole (MMI) and 100 mg potassium iodide (KI) (Fig. 3) per day. Her compliance was good and her signs and symptoms of hyperthyroidism improved within one month. Due to further normalization of laboratory results, KI was stopped and the dose of MMI was reduced to 5 mg per day (Fig. 3).

After nine months of treatment, the patient elected to undergo subtotal thyroidectomy. Histological examination of the surgical specimen showed multifocal lymphocytic infiltration and follicular hyperplasia, which were compatible with GD, and no evidence of malignancy. A hypothyroid state developed, but thyroid function finally normalized following treatment with 100 μ g of L-thyroxine (LT4) per day (Fig. 3).

Twin B is a 28-year-old woman. In April 2013, she began experiencing thirst and sweating, just like Twin A (Fig. 1). In July, she had palpitations and tremors in her fingers at rest and her body weight decreased with no change in appetite. In February 2014, she noticed dyspnea during the resting state. In May, she finally decided to consult her family doctor,

Figure 3. Clinical course of Twin A since her initial visit to our department. The shaded area indicates the normal range of free T3.

Table 1. Laboratory results of Twin A and Twin B before the initiation of therapy. The normal range is given in parentheses

	Twin A	Twin B	
fT3 (pg/mL)	24.8	23.0	(2.39-4.06 pg/mL)
fT4 (ng/dL)	9.26	7.52	(0.71-1.52 ng/dL)
TSH (μIU/mL)	< 0.01	< 0.01	(0.51-4.26 μIU/mL)
TRAb (IU/L)	> 30	> 30	(< 2.0 IU/L)
TPOAb (IU/mL)	137	207	(< 16 IU/mL)
TgAb (IU/mL)	537	570	(< 28 IU/mL)

TSH, Thyroid Stimulating Hormone; TRAb, TSH Receptor Antibody, TPOAb, Thyroid Peroxidase Antibody; TgAb, Thyroglobulin Antibody.

Table 2. Human leukocyte antigens (HLA) in this case; completely consistent because the patients are identical twins

HLA	Twin A	Twin B
A	11	11
	31	31
B	51	51
	67	67
C	*07:02:01	*07:02:01
	*14:02:01	*14:02:01
DRB1	*04:05	*04:05
	*16:02	*16:02
DQA1	*01:02/11	*01:02/11
	*03:03	*03:03
DQB1	*04:01:01	*04:01:01
	*05:02:01	*05:02:01
DPB1	*02:02	*02:02
	*05:01	*05:01

who suspected hyperthyroidism and referred her to our hospital.

Physical examination of Twin B revealed sinus tachycardia (113 bpm on ECG), no edema of the eyelid, and no ophthalmologic abnormalities, but with moist skin and diffuse goiter, as in Twin A. The Twin B's laboratory results and thyroid USG findings were very similar to those of Twin A (Table 1) (Fig. 2c and 2d), indicating hyperthyroidism. Twin B was also diagnosed with hyperthyroidism due to GD. She was

Figure 4. Clinical course of Twin B since her initial visit to our department. The shaded area indicates the normal range of free T3.

initially treated with 30 mg of MMI (Fig. 3) per day.

Twin B's compliance with medication was poor and her palpitations worsened within one month. We prescribed KI at 100 mg per day. One week later, her symptoms improved. After two months of treatment, serum fT3 and fT4 levels decreased to almost within the normal range. However, improvement in her symptoms led to poor compliance with medication again. Dosages had to be changed several times (Fig. 4). She visited our hospital at irregular intervals. It was difficult to induce remission with medication only. The patient contemplated surgical therapy but remained hesitant. We performed HLA-A, HLA-B, HLA-C, HLA-DRB1, HLA-DQA1, HLA-DQB1, and HLA-DPB1 genotyping in both twins: HLA-A11, HLA-A31, HLA-B51, HLA-B67, HLA-C*07:02:01, HLA-C*14:02:01, HLA-DRB1*04:05, HLA-DRB1*16:02, HLA-DQA1*01:02/11, HLA-DQA1*03:03, HLA-DQB1*04:01:01, HLA-DQB1*05:02:01, HLA-DPB1*02:02, and HLA-DPB1*05:01, with results shown in Table 2.

In the present case, the patients' father also developed GD at around age 28. We therefore considered performing HLA genotyping in him. However, the patients were separated from him when they were around 10 years old and we were unable to contact him.

DISCUSSION

We present a case of identical female twins who developed GD within a few months of each other and who had very similar laboratory results. The synchronous development of GD suggests a common trigger, which could be a very stressful family event or something similar. However, detailed diagnostic interviews with the patients revealed that there had been no preclinical stressful events in the patients' lives

before the onset of GD. We consider that the separation from patients' father is the past event 18 years prior to this report and is unlikely a common trigger in this case.

Many studies have reported that environmental factors such as diet and smoking influence the development of GD (1, 2, 8-10). In this case, both patients live in the same city and have smoked cigarettes for a long time, and their tastes in food are similar to those of other Japanese individuals who live in iodine-sufficient areas.

On the other hand, several twin studies have reported a higher concordance rate for AITD in identical twins than in non-identical twins (11, 12). Therefore, in this case we also considered the influence of genetic factors on the onset and course of GD.

Several AITD susceptibility genes have been reported, such as TR, Tg, TPO, HLA, cytotoxic T lymphocyte antigen 4, and protein tyrosine phosphatase non-receptor type 22 (1, 2, 13-15). For these candidate genes, a number of epidemiological studies have reported an association between HLA haplotype and GD in several races (1, 2, 16-19). Thus we performed HLA genotyping in this case, with results shown in Table 2. The twins had at least three susceptibility genes for GD: HLA-DPB1*05:01, DRB1*04:05, and DQB1*04:01 (Table 2).

Several Japanese epidemiological studies have determined that HLA-DPB1*05:01 confers susceptibility to GD (20-24). Dong *et al.* performed HLA genotyping in 317 Japanese patients with GD (24), and showed that HLA-A2, HLA-B46, HLA-Cw11, and HLA-DPB1*05:01 were associated with GD. They conducted further analyses that showed that the odds ratio for GD in DPB1*05:01-positive, A2-negative patients and DPB1*05:01-negative, A2-positive patients were 4.4 and 2.2, respectively. Interestingly, in individuals who are positive for both HLA-A2 and DPB1*05:01, the odds ratio for developing GD was as high as 10.5. Based on these results, Dong and colleagues hypothesized that HLA-A2 and DPB1*05:01 synergistically contributed to the development of GD.

Previous studies reported that the timing of onset of GD was associated with HLA alleles and haplotypes. Iwama *et al.* genotyped Japanese patients with GD that began in childhood onset or in adult onset, respectively (25). They showed that the prevalence of HLA-DRB1*04:05 and HLA-DQB1*04:01 was significantly higher in patients with childhood onset GD than in controls with adult onset GD. In our case, both twins had HLA-DRB1*04:05

and HLA-DQB1*04:01 (Table 2). In another study, Horiki *et al.* investigated HLA alleles in Japanese patients with early-onset myasthenia gravis (MG) and showed that DQB1*03 and DPB1*0201 contributed synergistically to the development of the conditions in females (26). Valdes *et al.* investigated the influence of HLA genotypes on age at the onset of type 1 diabetes in various populations of European descent, and showed that HLA information could predict some of the risk of both early and late onset of the disease (27).

Based on the fact that several HLA alleles have synergistic effects on disease development and the timing of onset, we hypothesize that the three susceptibility genes (HLA-DPB1*05:01, DRB1*04:05, and DQB1*04:01) identified in this case might act synergistically in GD development, including contributing to the short window between GD onsets in our patients.

In conclusion, we present a case of identical female twins who developed GD with very similar timing and clinical and laboratory results. In addition to having identical genetic backgrounds, similar environmental risk factors, and antibodies against thyroid tissue, we believe that three HLA susceptibility alleles for GD might have synergistically contributed to the close timing of GD onset. HLA genotype and epidemiologic analysis of further twin cases is expected to elucidate the pathogenesis of GD.

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Conflict of interest

The authors declare that they have no conflict of interest concerning this article.

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