

Clinical Features of Patients with Basedow's Disease and High Serum IgG4 Levels

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Abstract

Objective IgG4-related disease is a recently characterized condition presenting with high blood IgG4 levels, swelling of organs, and hypertrophic lesions. This disease is associated with thyroid disease, Hashimoto's disease, and Riedel's thyroiditis. However, there is little information on the association between IgG4-related disease and Basedow's disease. We herein defined the clinical features of patients with Basedow's disease and high IgG4 levels.

Methods We compared two groups of patients with Basedow's disease (n=72) who had either normal IgG4 levels (<135 mg/dL; n=67) or high IgG4 levels (≥135 mg/dL; n=5 [6.9%], mean IgG4: 206±116 mg/dL, IgG4/IgG ratio: 10.6%±3.3%).

Patients Seventy-two newly diagnosed, untreated patients with Basedow's disease.

Results Compared to the normal IgG4 group, patients in the high IgG4 group were predominantly male and showed a significantly higher thyroid low-echo score (1.8±0.4 vs. 1.2±0.5) and eosinophil count (363±354/mm² vs. 136±122/mm²). Five patients had high IgG4 levels: one had a pancreatic lesion, and four had thyroid lesions.

Conclusion Patients with Basedow's disease and high IgG4 levels may represent a new subtype of Basedow's disease. Further studies with larger sample sizes are needed.

Key words: IgG4, IgG4 thyroiditis, Basedow's disease, IgG4-related disease

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Introduction

IgG4-related disease (IgG4-RD) is a new disease concept proposed in Japan after the 2001 report on autoimmune pancreatitis by Hamano et al. (1). IgG4-RD is characterized by marked tissue infiltration of lymphocytes and IgG4-positive plasma cells and fibrosis of the infiltrated area, which lead to swelling and nodular/hypertrophic lesions of organs throughout the body. These features may occasionally be accompanied by severe complications such as obstructive/compressive symptoms (due to organ swelling and hypertrophy) and organ failure (due to cell infiltration and fibrosis) (2).

Several recent studies have highlighted the relationship between IgG4-RD and thyroid disease, Hashimoto's disease, Riedel's thyroiditis, Basedow's disease, and other dis-

eases (3-10). Li et al. (3) were the first to describe the clinical and histological findings characterizing IgG4 thyroiditis as a subtype of Hashimoto's disease. The histopathological findings in IgG4 thyroiditis include stromal fibrosis, lymphocyte infiltration, and increased numbers of IgG4-positive plasma cells. The affected patients are usually young men who show high thyroid autoantibody titers and diffuse low echo on ultrasonography, with many patients showing rapid thyroid destruction and fibrosis or presenting with subclinical hypothyroidism (4, 5). Furthermore, cases of Riedel's thyroiditis complicated with IgG4-RD affecting other organs have also been reported (6, 7). In addition, Takeshima et al. (8) reported IgG4-positive plasma cell infiltration in 2 of 10 cases of Riedel thyroiditis, which were histopathologically examined.

Patients with Basedow's disease present with elevated

IgG4 levels, and Basedow's disease-type IgG4 thyroiditis has been reported as a subtype of Basedow's disease (9, 10). However, many questions concerning the pathology of Basedow's disease-type IgG4 thyroiditis remain to be addressed, and its clinical features have not yet been established. The aim of the present retrospective study was to define the clinical features of Basedow's disease with elevated IgG4 levels and to compare them with those of Basedow's disease with normal IgG4 levels.

Materials and Methods

Patients

A cross-sectional study was carried out in 72 newly diagnosed untreated patients with Basedow's disease who were managed at the Outpatients Clinic of our Hospital between November 2011 and July 2015. The diagnosis of Basedow's disease was based on the Basedow's Disease Diagnostic Guidelines prepared by the Japan Thyroid Association (11). Patients who had previously received treatment for Basedow's disease, patients with malignant tumors, pregnant or possibly pregnant women, and lactating women were excluded from the study. The study received approval from the Ethics Committee of the University of Occupational and Environmental Health. Patients were informed of the study design in writing and their consent was obtained.

Collection of clinical information

Medical records were accessed to obtain data on patients' age; gender; IgG4, IgG, total protein, and serum albumin levels; eosinophil count; thyroid function; thyroid autoantibody (TRAb) levels; and ultrasound findings. The IgG4-related Disease Comprehensive Diagnostic Criteria (2011) defines serum IgG4 level ≥ 135 mg/dL as an abnormal blood IgG4 elevation (2); according to this criterion, the study subjects were divided into two groups: patients with elevated IgG4 levels (IgG4 ≥ 135 mg/dL) and those with normal IgG4 levels (IgG4 < 135 mg/dL). The clinical features of the two groups were compared and analyzed.

Laboratory tests

Serum IgG and IgG4 levels were measured by immunonephelometry (SRL, Tokyo, Japan), with the reference range set at 870-1,700 mg/dL for IgG and 4.8-105 mg/dL for IgG4. Serum free triiodothyronine (fT3) and free thyroxine (fT4) levels were measured quantitatively by the electrochemiluminescence method (ECLIA), with the reference ranges set at 2.47-4.34 pg/mL, 0.97-1.79 ng/dL, and 0.34-6.50 μ U/mL for fT3, fT4, and thyroid stimulating hormone (TSH), respectively. TRAb levels were measured by ECLIA (ECLusys Reagent TRAb). Thyroglobulin autoantibodies (TgAbs) and thyroid peroxidase antibodies (TPOAbs) were measured by ECLIA (ECLusys Reagent Anti-Tg/Anti-TPO), with the reference ranges set at TRAb ≤ 2.0 IU/L, TgAb < 28.0 IU/mL, and TPOAb < 16 IU/mL.

Ultrasonography

Ultrasonography was performed with an APLIO XG SSA-790A (Toshiba Medical Systems Corporation, Tochigi, Japan) combined with a 7.5-MHz linear electronic scan probe PLT-604AT (Toshiba Medical Systems Corporation). Low echogenicity of the thyroid was rated on a four-grade scale, as described by Yoshida et al. (12): Grade 0, diffuse high-amplitude echoes throughout the lobe of the thyroid; Grade 1, low-amplitude and nonuniform echoes in the whole or several regions of the thyroid; Grade 2, several sonolucent regions in the thyroid; and Grade 3, no apparent echoes or very-low-amplitude echoes throughout the thyroid. The peak systolic velocity (PSV) of the superior thyroid artery (STA), as a marker of thyroid blood flow status, was measured. The sample volume was set at the middle of the vessel, and the Doppler angle was adjusted to $\leq 60^\circ$. The STA-PSV values of the left and right lobes of the thyroid were averaged to obtain the mean STA-PSV. Transverse scanning was conducted to maximize the anteroposterior and transverse dimensions, followed by calculation of the size of each thyroid lobe in mm² using the following formula: anteroposterior dimension \times transverse dimension. The summed sizes of the right and left lobes were adapted as the thyroid size.

Statistical analysis

All values are expressed as the mean \pm standard deviation (SD) values. Fisher's exact test was used to assess data in the two-dimensional contingency tables for comparisons based on sex. The Mann-Whitney U-test was used to compare two individual groups. Data for TRAb, TgAb, and TPOAb were analyzed with log-transformed values. The level of significance was set at $p < 0.05$. The SPSS Statistical Software program, ver. 21.0 (SPSS Inc., Chicago, IL, USA) was used for all statistical analyses.

Results

Serum IgG4 and IgG levels

Table 1 shows the clinical features of the 72 patients. The mean IgG4 level was 49.3 ± 57.8 mg/dL (range: 3-411 mg/dL), and the IgG4/IgG ratio was $3.3\% \pm 2.8\%$ (range: 0.3-13.7%). Five (6.9%) patients were allocated to the high IgG4 group (≥ 135 mg/dL), with a mean IgG4 level of 206.0 ± 115.8 mg/dL (range: 138-411 mg/dL) and IgG4/IgG ratio of $10.6\% \pm 3.3\%$ (range: 5.7-13.7%). The IgG4/IgG ratio was significantly higher in the high IgG4 group than in the normal IgG4 group ($p < 0.001$).

An analysis based on sex showed a significantly higher proportion of male patients in the high IgG4 group (four men and one woman) than in the normal IgG4 group (16 men and 51 women) ($p = 0.019$), and 20% of all male patients were allocated to the high IgG4 group. There were no significant differences between the two groups with regard to the mean age and serum fT3, fT4, TRAb, TgAb, and

Table 1. Clinical Features of Patients with Basedow's Disease.

	All (n=72)		normal IgG4 (<135 mg/dL; n=67)		high IgG4 (≥135 mg/dL; n=5)		p value
	Mean±SD (range)	n	Mean±SD (range)	n	Mean±SD (range)	n	
Sex (M/F)	20/52		16/51		4/1		0.019
Age (years)	41.9±15.7 (15-78)	72	41.9±15.6 (15-78)	67	43.0±18.7 (24-68)	5	0.982
Immunoglobulin G (mg/dL)	1,375±388 (658-3,157)	72	1,330±303 (658-2,676)	67	1,977±819 (1,158-3,157)	5	0.053
Immunoglobulin G4 (IgG4) (mg/dL)	49.3±57.8 (3-411)	72	37.5±27.1 (3-127)	67	206.0±115.8 (138-411)	5	<0.001
IgG4 / IgG (%)	3.3±2.8 (0.3-13.7)	72	2.8±1.9 (0.3-9.2)	67	10.6±3.3 (5.7-13.7)	5	<0.001
Thyroid size on ultrasound (mm)	18.5±4.9 (9.5-38.0)	72	18.2±4.8 (9.5-38.0)	67	21.4±6.4 (15.0-29.0)	5	0.270
Degree of hypoechogenicity	1.3±0.6 (0-2)	72	1.2±0.5 (0-2)	67	1.8±0.4 (1-2)	5	0.017
Mean velocity in the STA (cm/s)	74.8±35.0 (17.0-191.5)	72	76.1±35.5 (17.0-191.5)	67	58.5±24.3 (35.0-96.0)	5	0.262
Free triiodothyronine (fT3) (pg/mL)	16.9±8.3 (3.7-32.6)	61	16.7±8.3 (3.7-32.6)	56	18.9±9.3 (9.6-30.2)	5	0.545
Free thyroxine (fT4) (ng/dL)	5.0±1.9 (1.6-7.8)	72	4.9±1.9 (1.6-7.8)	67	5.7±2.2 (3.0-7.8)	5	0.374
TRAb (IU/L)	17.1±22.4 (0.3-141.2)	72	16.4±21.3 (0.3-141.2)	67	25.4±36.3 (1.3-88.7)	5	0.807
TgAb (IU/mL)	336±754 (6-4,000)	72	330±783 (10-4,000)	57	394±281 (12-774)	5	0.201
TPOAb (IU/mL)	221±222 (6-600)	71	207±219 (6-600)	56	376±221 (8-564)	5	0.179
Total protein (mg/dL)	7.1±0.6 (5.8-8.4)	65	7.0±0.5 (5.8-8.2)	60	7.7±0.5 (7.1-8.4)	5	0.016
Albumin (mg/dL)	4.0±0.4 (3.1-4.7)	70	4.0±0.4 (3.2-4.7)	65	3.9±0.6 (3.1-4.6)	5	0.766
Total protein/globulin	1.3±0.3 (0.6-2.3)	65	1.3±0.2 (0.8-2.3)	60	1.1±0.5 (0.6-1.8)	5	0.074
Leukocyte count (×10 ³ /mm ³)	5.6±2.0 (3.1-13.7)	70	5.5±2.0 (3.1-13.7)	65	6.8±2.6 (4.8-10.8)	5	0.197
Eosinophil count (/mm ³)	153±158 (16-988)	67	136±122 (16-577)	62	363±354 (110-988)	5	0.015

p values by Fisher's exact test or Mann-Whitney U-test, significant differences are marked in bold.

Thyroid size was measured on ultrasound as the sum of both lobes using the following equation: anteroposterior×transversal diameters (mm²) at the maximum position.

Degree of thyroid hypoechogenicity was classified into Grades 0-3 [12]. Grade 0: diffuse high-amplitude echoes throughout the whole lobe of the thyroid, Grade 1: low-amplitude and nonuniform echos in the whole or several regions of the thyroid, Grade 2: several sonolucent regions in the thyroid, Grade 3: no apparent echoes or very low amplitude echoes throughout the whole thyroid.

Values of >7.8, >32.6, >600 and >4,000 were used in calculations as 7.8, 32.6, 600 and 4,000, respectively.

STA: superior thyroid artery, TRAb: thyroid stimulating hormone receptor antibody, TgAb: thyroglobulin autoantibodies, TPOAb: thyroid peroxidase antibody

TPOAb levels.

Ultrasonography showed a significantly higher low-echo score (higher degree of hypoechogenicity) in the high IgG4 group than in the normal IgG4 group (1.2±0.5 vs. 1.8±0.4, p=0.017). There were no significant inter-group differences in thyroid size or mean STA-PSV. Furthermore, the TP and eosinophil count were significantly higher in the high IgG4 group than in the normal IgG4 group (p=0.016 and p=0.015, respectively).

Clinical features of patients with high serum IgG4 levels

Table 2 summarizes the clinical features of the five patients with high serum IgG4 levels. Four had a high IgG4/IgG ratio (≥8%). Patient 2 had a TRAb level of ≤ 2.0 IU/L, and iodine scintigraphy allowed the diagnosis of Basedow's disease. One patient (Patient 1) had a pancreatic lesion, but the remaining four were free of other systemic complications.

Discussion

To our knowledge, there are few published reports of serum IgG4 levels in newly diagnosed, untreated patients with Basedow's disease. Our results showed high IgG4 levels in 6.9% of patients with Basedow's disease. Patients with high

IgG4 levels were mostly young male patients with hypereosinophilia and a large thyroid low-echo area. Cases of Basedow's disease with high IgG4 levels have been reported in recent years (9, 10). Takeshima et al. (10) reported IgG4 levels of ≥135 mg/dL in 7 of 109 patients with Basedow's disease. Similarly, in the present study, high IgG4 levels were found in 6.9% of 72 Basedow's disease patients. In the study of Takeshima et al., there was no marked difference in the male-to-female ratio between the elevated and non-elevated IgG4 groups. Thyroid ultrasonography revealed increased hypoechogenic areas, but no marked differences were observed in the anti-TSH receptor antibody levels or thyroid function. In contrast, the high IgG4 group in the present study demonstrated a higher proportion of men. Of note, our study was the first to include an analysis of eosinophil levels.

The incidence of Basedow's disease is 5-10 times higher in women than in men (13), and the incidence of Hashimoto's disease is 8-9 times higher in women than in men (14). Furthermore, autoimmune thyroiditis is commonly reported more frequently in women than in men. However, the reported incidence of IgG4-RD is higher in men than in women (15). Li et al. (16) also reported a higher percentage of men with Hashimoto's disease-type IgG4 thyroiditis. In addition, in the present study, men comprised a higher proportion of cases with elevated IgG4 level, suggesting that

Table 2. Clinical Features of the Five Patients with High Serum Immunoglobulin G4 Level.

	Patient 1	Patient 2	Patient 3	Patient 4	Patient 5
Sex	F	M	M	M	M
Age (years)	56	68	28	39	24
Immunoglobulin G (mg/dL)	3,157	2,475	1,158	1,583	1,511
Immunoglobulin G4 (IgG4) (mg/dL)	411	142	159	138	180
IgG4 / IgG (%)	13.0	5.7	13.7	8.7	11.9
Thyroid size on ultrasound (mm)	18.5	15	17	27.5	29
Degree of hypoechogenicity	2	1	2	2	2
Mean velocity in the STA (cm/s)	61	38.9	35.0	61.5	96.0
Free triiodothyronine (fT3) (pg/mL)	10.06	26.03	9.62	18.44	30.17
Free thyroxine (fT4) (ng/dL)	4.12	7.77	2.98	5.99	7.77
TRAb (IU/L)	13.1	1.3	3.0	20.7	88.7
TgAb (IU/mL)	773.6	511.8	390	12.2	285.0
TPOAb (IU/mL)	530.0	564.1	393.9	8.5	384.0
Total protein (mg/dL)	8.4	8.1	7.1	7.3	7.7
Albumin (mg/dL)	3.1	3.8	4.6	3.7	4.2
Total protein/globulin	0.58	0.88	1.84	1.03	1.2
Leukocyte count ($\times 10^3/\text{mm}^2$)	10,800	5,200	5,100	8,300	4,800
Eosinophil count (/mm ²)	238	208	270	988	110

Thyroid size on ultrasound represented the sum size of both lobes, calculated by: anteroposterior \times transversal diameters (mm²) at the maximum position.

Degree of hypoechogenicity in the thyroid was classified into Grade 0-3 [9]. Grade 0: diffuse high-amplitude echoes throughout the whole lobe of the thyroid, Grade 1: low-amplitude and nonuniform echos in the whole or several regions of the thyroid, Grade 2: several sonolucent regions in the thyroid, Grade 3: no apparent echoes or very low amplitude echoes throughout the whole thyroid.

See Table 1 for abbreviations.

IgG-related thyroiditis is more common in men than in women. Furthermore, our results showed that 20% of all male patients with Basedow's disease had high IgG4 levels. Therefore, physicians should be aware of IgG4-related thyroiditis in men with the above conditions.

Diffuse low-level echoes have been reported in a high percentage of patients with Hashimoto's disease-type IgG4 thyroiditis (17, 18). A low-echo area is considered to reflect thyroid destruction and fibrosis (16, 18). Furthermore, large low-echo areas, similar to the ones observed in the present study, have been reported in patients with Basedow's disease and high IgG4 levels (10). Nishihara et al. (9) reported a case of Basedow's disease with markedly high numbers of IgG4-positive plasma cells as a pathological feature, accompanied by marked fibrosis of the thyroid tissue and lymphocyte/plasma cell infiltration. Thus, a low-echo area is considered to result from lymphocyte infiltration, stromal tissue fibrosis, and eosinophilic changes.

In patients with IgG4-RD, the affected area often shows infiltration by eosinophils, lymphocytes, and IgG4-positive plasma cells; an increase in the peripheral blood IgE level (2) and peripheral blood hypereosinophilia (19) is also observed. Although no such findings in patients with Basedow's disease have been published to date, the present study demonstrated a higher peripheral blood eosinophil count in Basedow's disease patients with high IgG4 levels than in those with normal IgG4 levels. While the exact etiology of IgG4-RD disease remains unclear, the presence of high lev-

els of Th2-related cytokines (interleukin [IL]-4, IL-5, and IL-13) in the affected areas (20) suggests that these cytokines trigger the increase in IgE or eosinophil levels. While Th2-related cytokines mediate allergic responses (21), IgG4-RD is frequently complicated with eosinophilia, asthma associated with increased IgE levels, and allergic rhinitis (22). The allergic mechanism is considered to be associated with the pathogenesis of IgG4-RD.

The pathology of IgG4-RD includes synchronous or metachronous swelling and nodular/hypertrophic lesions of systemic organs, in addition to autoimmune abnormalities and high peripheral blood IgG4 levels. Yamamoto et al. (23) found lesions in multiple organs in 61.4% of patients with IgG4-RD. However, Hashimoto's disease-type IgG4 thyroiditis does not involve other organs (5), and an analysis of 149 cases with Hashimoto's disease by Takeshima et al. (24) detected extra-thyroid lesions in only 2 patients. Furthermore, cases of Basedow's disease with high IgG4 levels reported previously had no complications in any organ other than the thyroid (9, 10), and the present study suggested a low incidence (i.e. one in five patients) of complications affecting organs other than the thyroid.

Several limitations associated with the present study warrant mention. First, tissue biopsies and histopathological examinations were not conducted in any of the patients. This study was designed to evaluate patients with Basedow's disease at the time of diagnosis and before any treatment. All patients showed an enhanced thyroid function. Therefore, it

was difficult to conduct invasive tests such as a tissue biopsy. Second, IgG4 levels were not examined over time. Evaluations that also include a tissue biopsy and histopathological examination, together with an analysis of the long-term changes in IgG4 levels in these patients, should therefore be conducted in the future.

Conclusion

In conclusion, the present study demonstrated the presence of high IgG4 levels in 6.9% of the sample population with Basedow's disease. These were mostly young male patients with large thyroid low-echo areas and hypereosinophilia, which suggests that Basedow's disease with a high IgG4 level is a new subtype of Basedow's disease characterized by unique clinical features. The mechanisms underlying these clinical features remain obscure. Further studies on additional cases of the disease, including immunological and histopathological evaluation, should facilitate the establishment of this condition as a separate disease entity and allow for a detailed discussion of its pathophysiology and treatment.

The authors state that they have no Conflict of Interest (COI).

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