High serum IgG4 concentrations in patients with Hashimoto thyroiditis.

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BACKGROUND

Hashimoto thyroiditis (HT, synonyms: chronic lymphocytic thyroiditis, chronic autoimmune thyroiditis) - an autoimmune disease described for the first time more than a hundred years ago. Despite a great progress made in identifying factors responsible for the development of autoimmune inflammation, the pathogenesis of HT still remains unclear. However, recent reports strongly suggest that at least some cases of HT may be closely associated with IgG4-related disease (IgG4-RD).

Clinically, IgG4-RD is characterized by high serum immunoglobulin class G4 (IgG4) levels and alleviation of symptoms after steroid therapy. Furthermore, irrespective of the organs affected, IgG4-RDs share similar pathologic features, including lymphoplasmacytic infiltration, fibrosis, obliterative phlebitis, and increased numbers of IgG4-positive plasma cells. In 2012 (1), a group of researchers suggested that on the basis of immunostaining for IgG4, HT can be divided into two groups, which were proposed as IgG4 thyroiditis and non-IgG4 thyroiditis. What is more, since increased IgG4 concentration (>134 mg/dl) was observed in the majority (70-90%) of IgG4-RD patients, the measurement of serum IgG4 level was proposed as a useful method of distinguishing IgG4 thyroiditis from non-IgG4 thyroiditis.

AIM

In the present study we aimed to find out, whether the measurement of serum IgG4 concentration allows for an identification of distinct types of HT, with different clinical, sonographic and serologic characteristics.

MATERIAL AND METHODS

The study comprised 81 subjects, including 53 patients with diagnosed HT (mean age 44.6 15.3 years, F/M 90.6%/9.4%) and 28 healthy individuals (mean age 40.8 15.6 years, F/M 89.3%/10.7%), matched for age and gender.
None of the participants was suspected/diagnosed of having any IgG4-RD (except IgG4-HT).
All the patients underwent thyroid ultrasonography to establish thyroid volume, echogenicity, vascularity (with Power Doppler method), signs of fibrosis and calcification.
Serum TSH concentration was measured using an enzyme-linked immunoassay *(DiaSource, Louvain-la-Neuve, Belgium)*.
Anti-peroxidase antibodies (TPOAb) and tumor necrosis factor – alpha (TNFα) concentrations were also determined by commercial immunoassays (*Euroimmun, Lubeck, Germany and R&D Systems, Minneapolis, USA*).
The concentration of anti-TSH receptor antibodies (TRAb) was measured by a commercial radioimmunoassay *(TRAK HUMAN, B-R-A-H-M-S Berlin, Germany)*.
IgG4 was estimated using Human IgG4 Platinum ELISA *(eBioscience, Vienna, Austria)*.
The following chamokines and apoptotic markers were also measured: Human Fas Ligand /TNFSF6, Human TRAIL/TNFSF10, Human TGF-β1 and chemokines CXCL9/I-TAC, CXCL10/IP-10 and CXCL11/I-TAC (*Human Quantikine ELISA R&D Systems, Minneapolis, USA*).

STATISTICA 10.0 for Windows (StatSoft.Inc, USA) and IBM SPSS Statistics 21.0 (Predictive Solutions, USA). Prior to the analysis, data were tested for normality of distribution using Kołmogorow-Smirnow test with Lillefors correction and Shapiro-Wilk test. Differences between the groups were compared by U Mann-Whitney test. P value lower than 0.05 was considered statistically significant.

RESULTS

1. The HT group was divided into IgG4-HT (IgG4>135 IU/ml) and non-IgG4-HT (IgG4<135 IU/ml), depending on the patient's IgG4 concentration.
The group with IgG4>135 IU/ml accounted for 32.5% of all HT patients.
The percentage of male patients was 7.5% in the non-IgG4-HT and 18.2% in the group with a high level of IgG4.

2. Mean HT duration was 4.9_4.6 years in non-IgG4-HT group and 2.5_1.96 in IgG4-HT group (p<0,001). Furthermore, the IgG4-HT patients required higher L-thyroxine dose in order to reach euthyreosis in comparison with the non-IgG4-HT group.

3. The medical history of IgG4-HT patients revealed no presence of autoimmune disorders, whereas 15% of patients from the non-IgG4-HT group had other autoimmune diseases, such as vitiligo (7.5%), type 1 diabetes and celiac disease (2.5%).

4. Ultrasound examination revealed a frequent occurrence of decreased echogenicity of the thyroid in both non-IgG4-HT and IgG4-HT patients (86.1% vs 81.8%), as well as a comparable percentage of thyroid calcifications (9.1% vs 13.9%).

- The signs of fibrosis were present in 27.0% of IgG4-HT patients in comparison with 9,1% of the non-IgG4-HT group, but the difference was not significant.
- The non-IgG4-HT patients had a lower number of thyroid nodules compared with IgG4-HT patients (p=0.02), and 66,7% of all nodules were hypoechogenic

Ultrasonographic and biochemical characteristics of the patients with non-IgG4-HT, IgG4-HT and the control group.

	non-IgG4-HT- IGg 4<135IU/ml n=40	IgG4-HT IGg 4>135IU/ml n=13	p	Control group n=28	p*
Thyroid volume (ml)	12.1 (7.9-14.9)	13.0 (10,1-17,2)	ns	18.5(12.5-19.5)	0.001
Thyroid nodules (n)	1.0 (1.0-2.0)	2.0 (1.0-2.0)	0.02	-	
TSH (IU/ml)	1.5 (0.98-1.9)	1.2 (0.95-2.1)	ns	1.1 (0.9-1.4)	
TPOAb (IU/l)	248.3 (40.4-413.3)	11.0 (4.6-294.9)	0.02	6.1(4.9-10.2)	0.00001
TRAb (IU/l)	1.1 (0.8-1.3)	1.3 (0.8-1.7)	ns	0.3 (0.3-0.5)	0.00001
Levothyroxine dose (ug/day)	50.0 (0.-81.3)	75.0 (50.0-88.0)	ns		

Pro-inflammatory cytokines and apoptotic markers in the patients with non-IgG4-HT, IgG4-HT and the control group.

	non-IgG4-HT IgG 4<135IU/ml n=40	IgG4-HT IgG 4>135IU/ml n=13	p	Control group n=28	P*
IgG4 (IU/ml)	60.1 (25.3-75.9)	163.6 (135.5-208.7)	0.001	96.3 (42.7-112.2)	ns
TGF β1(pg/ml)	30361 (26019-32897)	33732 29897-36800)	0.05	32293 (29017-38791)	ns
TNFα (pg/ml)	5.7 (5.0-7.2)	6.1 (5.6-8.2)	ns	5.3 (4.1-6.4)	0.01
TRAIL (pg/ml)	109.2 (93.2-133.7)	110.3 (83.8-113.3)	ns	107.2 (87.3-129.6)	ns
FAS Ligand (pg/ml)	90.3 (76.6-104.9)	82.5 (74.2-130.2)	ns	87.7 (68.4-111.7)	ns
CXCL9 (pg/ml)	70.6 (52.7-95.7)	88.7 (69.1-116.4)	ns	62.7 (51.3-92.5)	ns
CXCL10 (pg/ml)	94.7 (79.9-120.7)	95.3 (77.4-130.2)	ns	96.0 (96.3-129.6)	ns
CXXL11 (pg/ml)	59.8 (24.7-77.2)	52.5 (24.7-63.4)	ns	56.2 (37.2-110.0)	ns

Data are shown as medians (interquartile range), differences between groups were tested by Mann-Whitney U test. p- between IgG4-HT and non-IgG4-HT, p- between IgG4-HT and control group.*

CONCLUSIONS:

Our results suggest that the measurement of serum IgG4 allows for an early identification of patients with more rapidly progressing and destructive form of HT, who require higher doses of L-thyroxine.
A relatively low TPOAb level and the absence of co-existing autoimmune diseases may suggest a distinct pathomechanism of this type of thyroiditis.

REFERENCES

1. Umehara H[1], Okazaki K, Masaki Y, Kawano M, Yamamoto M, Saeki T, Matsui S,Yoshino T, Nakamura S, Kawa S, Hamano H, Kamisawa T, Shimosegawa T,Shimatsu A, Nakamura S, Ito T, Notohara K, Sumida T,Tanaka Y, Mimori T, Chiba T, Mishima M, Hibi T, Tsubouchi H, Inui K, Ohara H.Comprehensive diagnostic criteria for IgG4-related disease (IgG4-RD). Mod. Rheumatol.2012;22(1):21-30

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