THE ASSOCIATION OF OTHER AUTOIMMUNE DISEASES IN PATIENTS WITH AUTOIMMUNE THYROIDITIS: REVIEW OF THE LITERATURE AND REPORT OF A LARGE SERIES OF PATIENTS.

Poupak Fallahi[1], Silvia Martina Ferrari[1],

Ilaria Ruffilli[1], Giusy Elia[1], Marco Biricotti[2],

Roberto Vita[3], Salvatore Benvenga[3,4,5], Alessandro Antonelli[1]

[1] Department of Clinical and Experimental Medicine, University of Pisa, Via Savi 10, 56126 Pisa, Italy;

[2] Department of Surgical, Medical, Molecular Pathology and Critical Area, University of Pisa, Via Savi 10, 56126 Pisa , Italy;

[3] Department of Clinical and Experimental Medicine, University of Messina, Policlinico G. Martino, Padiglione H, 4 piano, via Consolare Valeria, 98125, Messina, Italy;

[4] Master Program on Childhood, Adolescent and Women's Endocrine Health, University of Messina School of Medicine, Messina, Italy;

[5] Interdepartmental Program of Molecular and Clinical Endocrinology, and Women's Endocrine Health, University Hospital Policlinico G. Martino, Messina, Italy.

Corresponding author and person to whom reprint requests should be addressed:
Alessandro Antonelli, Prof.
Department of Clinical and Experimental Medicine
University of Pisa
Via Savi 10, I-56126, Pisa, Italy
Phone: +39-050-992318
Fax: +39-050-553235
e-mail: alessandro.antonelli@med.unipi.it

Abstract

We have evaluated prospectively the prevalence of other autoimmune disorders in outpatient clinic in 3069 consecutive patients with diagnosed chronic autoimmune thyroiditis (AT), with respect to two age- and sex-matched control groups: a) a control group of 1023 subjects, extracted from a random sample of the general population without thyroid disorders; b) 1023 patients with non-toxic multinodular goiter extracted from the same random sample of the general population, with similar odine intake. The results of our study demonstrate a significant increase of the prevalence of autoimmune disorders in AT patients (with respect to both controls), for the following diseases: chronic autoimmune gastritis (CAG), vitiligo (Vit), rheumatoid arthritis, polymialgia rheumatica (Polym), celiac disease, diabetes, sjogren disease, multiple sclerosis, systemic lupus erythematosus, sarcoidosis, alopecia, psoriathic arthritis, systemic sclerosis, HCV-related cryoglobulinemia. While the statistical analysis reached near the significance for Addison's disease and ulcerative colitis. Interestingly, the association of three autoimmune disorders was observed almost exclusively in AT patients, and the most frequent associations were AT+CAG+Vit and AT+CAG+Polym.

We suggest that patients with AT who remain unwell, or who develop new not specific symptoms (despite adequate treatment) should be screened for other autoimmune disorders, avoiding the delay in the diagnosis of these disorders.

Key words: Autoimmune thyroid diseases, autoimmune thyroiditis, hypothyroidism, AbTPO, Organ specific autoimmune diseases, Systemic rheumatological disorders.

Take-home messages:

- Associations exist between autoimmune thyroid diseases (AITD) and other organ specific, or systemic autoimmune disorders.
- However, the small sample sizes and the use of control populations not matched for age, or gender, or geographic location, might have hampered the results of several studies.
- Our study demonstrate a significant increase of the prevalence of autoimmune disorders in AT patients (with respect to two age and gender matched controls, of same geographic area), for the following diseases: chronic autoimmune gastritis, vitiligo, rheumatoid arthritis , polymyalgia rheumatica, celiac disease, diabetes, sjogren disease, multiple sclerosis, systemic lupus erythematosus, sarcoidosis, alopecia, psoriathic arthritis, systemic sclerosis, HCV-related cryoglobulinemia.
- The statistical analysis reached near the significance for Addison's disease and ulcerative colitis.
- The association of three autoimmune disorders was observed almost exclusively in AT patients, and the most frequent associations were autoimmune thyroiditis+ chronic autoimmune gastritis+vitiligo and autoimmune thyroiditis+ chronic autoimmune gastritis+ polymyalgia rheumatica.
- We suggest that patients with AT, being still unwell, or developing new not specific symptoms (though adequate treatment) should be screened for other autoimmune disorders, avoiding the delay in the diagnosis of these ones.

1. Introduction

Associations exist between autoimmune thyroid diseases (AITD) and other organ specific, or systemic autoimmune disorders [1-3].

Thyroid function abnormalities and thyroid autoantibodies have been frequently described in patients with systemic rheumatological autoimmune diseases, as Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus and systemic sclerosis [1, 4, 5].

Recent studies showed a greater prevalence of the association between AITD and rheumatic diseases [as Sjögren's syndrome, rheumatoid arthritis, systemic lupus erythematosus, systemic sclerosis, mixed cryoglobulinemia, sarcoidosis, or psoriathic arthritis], highlighting the possibility of common pathogenic mechanisms among them [4, 6-8].

More recently, a first study has evaluated longitudinally the incidence of new cases of thyroid autoimmunity and dysfunction in female patients with systemic sclerosis showing a high incidence of new cases of hypothyroidism, thyroid dysfunction, anti-thyroperoxidase (AbTPO) positivity. The appearance of hypothyroidism was related to a borderline high initial thyroid-stimulating hormone level, AbTPO positivity, and a hypoechoic and small thyroid. This study suggests that these patients should have periodic thyroid function follow-up [9].

Many studies underline the importance of a common genetic susceptibility (HLA, etc) in patients with AITD and systemic autoimmunity [1-3]. Even environmental factors could be implicated in the association of autoimmune disorders [1].

Serum and/or tissue CXCL10 expression is increased in organ specific autoimmune diseases, as autoimmune thyroiditis (AT), Graves' disease, type 1 diabetes, and/or systemic rheumatological disorders (like rheumatoid arthritis, systemic lupus

erythematosus, systemic sclerosis, mixed cryoglobulinemia), underlining the importance of a common immunopathogenesis of these disorders, characterized by a Th1 prevalent autoimmune response [1]. These studies suggest that patients with systemic autoimmune disorders should have periodic thyroid follow-up.

Here we report our experience in a prospective study that evaluated the prevalence of other autoimmune disorders in subjects with AT.

2. Methods

2.1. Patients

From 1993 to 2008 we have evaluated prospectively the prevalence of other autoimmune disorders in outpatient clinic in 3069 consecutive Caucasian patients with diagnosed chronic AT (**Table 1**). The patients were referred to us by general practitioners or other hospitals because of the presence of circulating thyroid autoantibodies or hypothyroidism, or clinical suspicion of a thyroid disorder. The diagnosis of AT [10,11] was established from the clinical presentation (presence of a firm goiter, varying in size from small to very large, with a lobulated surface), thyroid hormones and thyroid autoantibodies measurements, and/or thyroid ultrasonography (decreased, dyshomogeneous echogenicity). The majority of these patients had a normal thyroid volume, some showed goiter (11%) or atrophic thyroiditis (9%). A minority of patients (5%) were submitted to fine-needle aspiration to exclude the presence of thyroid cancer or lymphoma; in these cases, cytology confirmed the presence of a lymphocytic infiltration.

2.2. Controls

Matched control groups were used **(Table 1)**.

The prevalence of autoimmune disorders was evaluated in two age- and sex-matched control groups (three patients/one control).

The first control group (n=1023) consisted in subjects extracted from a random sample of the general population from the same geographic area [12] in whom a complete thyroid work-up [history, physical examination, thyroid-stimulating hormone (TSH), free triiodothyronine (FT3), free thyroxine (FT4), anti-thyroglobulin (AbTg) and AbTPO antibodies measurements, and ultrasonography] was available, and excluded the presence of thyroid disorders.

A second control group comprised 1023 patients with non-toxic multinodular goiter (MNG) extracted from the same random sample of the general population. The majority of these patients had a normal thyroid volume, some showed goiter (28%).

In all patients and controls, a blood sample was collected in the morning, after overnight fasting, and serum was kept frozen until thyroid hormones, and thyroid autoantibodies measurements.

All study subjects gave their informed consent to the study, which was approved by the local Ethical Committee.

All patients and controls were submitted to thyroid ultrasonography and fine-needle aspiration, if necessary; cytology confirmed the absence of a malignancy.

Thyroid blood flow by color-flow doppler was also studied in all patients [13], and controls.

2.3. Laboratory evaluation

Thyroid function and thyroid autoantibodies were measured as previously described [10]. Circulating FT3 and FT4 were measured by commercial RIA kits (AMERLEX-MAB FT3/FT4 Kit; Amersham, UK). Serum TSH (DiaSorin, USA), AbTPO and

AbTg (ICN Pharmaceuticals, USA) were evaluated by IRMA methods. For AbTg, AbTPO, positivity was set at > 50, and >10 IU/mL, respectively.

2.4. Evaluation of other autoimmune diseases

Patients were interviewed by a specialist physician at enrollment into the study. A structured questionnaire was completed seeking other common autoimmune diseases in the patients and controls. Diagnoses of other autoimmune disorders also were based on patient recall, with verification in the index case through cross-checking with current records and medications by the recruiting physicians. Furthermore any diagnosis of autoimmune disease was verified by a specialist (rheumatology, dermatology, gastroenterology or internal medicine) and confirmed or not on the base of the criteria proposed by the scientific societies for each specific disease [14].

Only if there was a confirming evidence of coexisting autoimmune diseases the patient was considered positive for the specific disorder.

2.5. Data analysis

Values are given as mean ± SD for normally distributed variables. Mean group values were compared by using one-way analysis of variance (ANOVA) for normally distributed variables, otherwise by the Mann-Whitney U test. Proportions were compared by the $\chi 2$ test. Post-hoc comparisons on normally distributed variables were carried out using the Bonferroni-Dunn test.

3. Results

The thyroid evaluation of AT, and MNG patients vs. controls is reported in **Table 1**. About 26% of AT patients were hypothyroid, while no case of hypothyroidism was present in MNG patients and controls.

A high prevalence of autoimmune diseases was observed in AT patients (**Table 2**) in comparison with controls or MNG patients. The 10 most frequently observed autoimmune diseases in AT patients were: chronic autoimmune gastritis (2.8%), vitiligo (2.7%), rheumatoid arthritis (2.4%), polymyalgia rheumatica (1.4%), celiac disease (1.3%), diabetes (type 1) (1%), sjogren disease (0.9%), multiple sclerosis (0.9%), systemic lupus erythematosus (0.8%), sarcoidosis (0.6%).

A significant increase of the prevalence of autoimmune disorders in AT patients was observed, with respect to both control groups, for the following diseases: chronic autoimmune gastritis, vitiligo, rheumatoid arthritis, polymyalgia rheumatica, celiac disease, diabetes (type 1), sjogren disease, multiple sclerosis, systemic lupus erythematosus, sarcoidosis, alopecia, psoriathic arthritis, systemic sclerosis, hepatitis C virus (HCV)-related cryoglobulinemia. The statistical analysis reached near the significance for Addison's disease and ulcerative colitis, while no significant trend was observed for the other disorders.

The association of three autoimmune disorders was observed in 36 patients with AT, only in 1 subject in controls, and no MNG patient (**Table 3**). The most frequent associations were AT+chronic autoimmune gastritis (CAG)+vitiligo (Vit) and AT+CAG+ polymyalgia rheumatica (Polym).

4. Discussion

It is well known that AT can be associated with increased prevalences of type 1 diabetes [15], vitiligo [16], Addison's disease [17], and multiple sclerosis [18]. However, the small sample sizes and the use of control populations not matched for age, or gender, or geographic location, might have hampered the results of several studies [19].

More recently a cross-sectional multicenter study of 3286 UK Caucasian subjects (2791 with Graves' disease; 495 with Hashimoto's thyroiditis) evaluated the coexistence of autoimmune disorders by a structured questionnaire. The frequency of another autoimmune disorder was 14.3% in AT patients. The most prevalent autoimmune disorders in AT patients were rheumatoid arthritis, pernicious anemia, systemic lupus erythematosus, Addison's disease, celiac disease, and vitiligo [20].

With respect to the above mentioned paper, our study has some important strength points: 1) it is a prospective study; 2) the relative risk for each of the different autoimmune diseases was calculated by dividing the observed prevalence by the best estimate of UK population prevalence based on the current literature in the Boelaert study (that was lacking of an appropriate internal control group); 3) two control groups matched by age and gender (that are important risk factor for thyroid autoimmunity) are present in our study, ruling out the influence of these parameters on the final results; 4) a control group of subjects from the general population in whom a complete thyroid screening excluded the presence of thyroid autoimmune disorders permits to higlight the difference with AT patients; 5) a control group of patients with MNG without thyroid autoimmunity permits to exclude the possible influence of non autoimmune thyroid pathologies on the final results; 6) a higher number of AT patients (3069 vs. 495) were studied; 7) the presence of other autoimmune disorders was verified by a specialist (rheumatology, dermatology, gastrenterology or internal medicine) and confirmed or not on the base of the criteria proposed by the scientific societies for each specific disease (not on the base of a questionnaire); 8) a larger number of autoimmune diseases have been investigated.

The results of our study demonstrate a significant increase of the prevalence of autoimmune disorders in AT patients (with respect to both controls), for the following

diseases: chronic autoimmune gastritis, vitiligo, rheumatoid arthritis, polymyalgia rheumatica, celiac disease, diabetes, sjogren disease, multiple sclerosis, systemic lupus erythematosus, sarcoidosis, alopecia, psoriathic arthritis, systemic sclerosis, HCV-related cryoglobulinemia. While the statistical analysis reached near the significance for Addison's disease and ulcerative colitis. On the whole however an increased prevalence of autoimmune diseases in AT patients have been shown. The statistical significance for some of the other autoimmune disorders is difficult to be reached, because of the low prevalence of these disorders (for example primary biliary cirrhosis, or dermatomyositis, etc); so larger samples of patients are needed to confirm or not these associations.

Interestingly, the association of three autoimmune disorders was observed almost exclusively in AT patients, and the most frequent associations were AT+CAG+Vit and AT+CAG+Polym.

The influence of genetics on the association of different autoimmune disorders has been shown, in fact: a) there is significant clustering of autoimmune thyroid disease within families (40% to 50% of AT patients report another family member with AT) [21] ; b) a clear evidence arises from twin studies for Graves' disease [22] and AT [23] with concordance rates of 30-40% in monozygotic twins and 0-7% in dizygotic twins.

However the precise pathogenetic mechanisms are not known, and AT is believed to result from an interaction between the products of genes conferring susceptibility with various environmental triggers [24].

Immunopathological studies have shown that in target organs of patients with chronic AT, or Graves' ophthalmopathy, or type 1 diabetes, at the onset of these diseases, a prevalent Th1 immune profile is present, as reported from animal models and in

humans [25,26]. For example in the initial and active phase of mixed cryoglobulinemia, a predominant Th1 immune response is shown, that in the inactive phase switches to Th2 [27,28]. The predominance of a Th1 immune profile at the beginning of AT and other autoimmune disorders, and the effects of genetic and environmental conditions, could lead to the onset of autoimmune phenomena interesting various organs in the same subject [1,29,30].

In conclusion, we demonstrate a significant increased risk of other autoimmune diseases in patients with AT. We suggest that patients with AT, being still unwell, or developing new not specific symptoms (though adequate treatment) should be screened for other autoimmune disorders, avoiding the delay in the diagnosis of these ones.

References:

[1] Antonelli A, Ferrari SM, Corrado A, Di Domenicantonio A, Fallahi P. Autoimmune thyroid disorders. Autoimmun Rev 2015;14:174–180.

[2] Miyadera H, Tokunaga K . Associations of human leukocyte antigens with autoimmune diseases: challenges in identifying the mechanism. J Hum Genet 2015;60:697–702.

[3] Cho JH, Feldman M. Heterogeneity of autoimmune diseases: pathophysiologic insights from genetics and implications for new therapies. Nat Med 2015;21:730–738.

[4] Robazzi TC, Adan LF. Autoimmune thyroid disease in patients with rheumatic diseases. Rev Bras Reumatol 2012;52:417–430.

[5] Cooper GS, Stroehla BC. The epidemiology of autoimmune diseases. Autoimmun Rev 2003;2:119–125.

[6] Lu MC, Yin WY, Tsai TY, Koo M, Lai NS. Increased risk of primary Sjögren's syndrome in female patients with thyroid disorders: a longitudinal population-based study in Taiwan. PLoS One 2013;8:e77210.

[7] Milic VD, Radunovic G, Boricic I, Ognjanovic S, Petrovic R, Radak-Perovic M, et al. High prevalence of autoimmune thyroid disease in subjects with sicca symptoms without Sjogren's syndrome. Rheumatology (Oxford) 2013;52:754–755.

[8] Antonelli A, Ferri C, Fallahi P, Cazzato M, Ferrari SM, Sebastiani M, et al. Clinical and subclinical autoimmune thyroid disorders in systemic sclerosis. Eur J Endocrinol 2007;156:431–437.

[9] Antonelli A, Fallahi P, Ferrari SM, Mancusi C, Giuggioli D, Colaci M, et al. Incidence of thyroid disorders in systemic sclerosis: results from a longitudinal follow-up. J Clin Endocrinol Metab 2013;98:E1198–E1202.

[10] Antonelli A, Ferri C, Fallahi P, Ferrari SM, Frascerra S, Carpi A, et al. Alpha-chemokine CXCL10 and beta-chemokine CCL2 serum levels in patients with hepatitis C-associated cryoglobulinemia in the presence or absence of autoimmune thyroiditis. Metabolism 2008;57:1270–1277.

[11] Antonelli A, Fallahi P, Mosca M, Ferrari SM, Ruffilli I, Corti A, et al. Prevalence of thyroid dysfunctions in systemic lupus erythematosus. Metabolism 2010;59:896–900.

[12] Antonelli A, Fallahi P, Delle Sedie A, Ferrari SM, Maccheroni M, Bombardieri S, et al. High values of Th1 (CXCL10) and Th2 (CCL2) chemokines in patients with psoriatic arthtritis. Clin Exp Rheumatol 2009;27:22–27.

[13] Vitti P, Rago T, Mazzeo S, Brogioni S, Lampis M, De Liperi A, et al. Thyroid blood flow evaluation by color-flow Doppler sonography distinguishes Graves' disease from Hashimoto's thyroiditis. J Endocrinol Invest 1995;18:857–861.

[14] Cooper GS, Bynum ML, Somers EC. Recent insights in the epidemiology of autoimmune diseases: improved prevalence estimates and understanding of clustering of diseases. J Autoimmun 2009;33:197–207.

[15] Barker JM. Clinical review: Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. J Clin Endocrinol Metab 2006;91:1210–1217.

[16] Laberge G, Mailloux CM, Gowan K, Holland P, Bennett DC, Fain PR, et al. Early disease onset and increased risk of other autoimmune diseases in familial generalized vitiligo. Pigment Cell Res 2005;18:300–305.

[17] Kasperlik-Zaluska A, Czarnocka B, Czech W. High prevalence of thyroid autoimmunity in idiopathic Addison's disease. Autoimmunity 1994;18:213–216.

[18] Barcellos LF, Kamdar BB, Ramsay PP, DeLoa C, Lincoln RR, Caillier S, et al. Clustering of autoimmune diseases in families with a high-risk for multiple sclerosis: a descriptive study. Lancet Neurol 2006;5:924–931.

[19] Jenkins RC, Weetman AP. Disease associations with autoimmune thyroid disease. Thyroid 2002;12:977–988.

[20] Boelaert K, Newby PR, Simmonds MJ, Holder RL, Carr-Smith JD, Heward JM, et al. Prevalence and relative risk of other autoimmune diseases in subjects with autoimmune thyroid disease. Am J Med 2010;123:183.e1–183.e9

[21] Brix TH, Christensen K, Holm NV, Harvald B, Hegedüs L. A population-based study of Graves' disease in Danish twins. Clin Endocrinol (Oxf). 1998;48:397–400.

[22] Ringold DA, Nicoloff JT, Kesler M, Davis H, Hamilton A, Mack T. Further evidente for a strong genetic influence on the development of autoimmune thyroid disease: the California twin study. Thyroid 2002;12:647–653.

[23] Brix TH, Kyvik KO, Hegedus L. A population-based study of chronic autoimmune hypothyroidism in Danish twins. J Clin Endocrinol Metab. 2000;85:536–539.

[24] Tomer Y, Davies TF. Searching for the autoimmune thyroid disease susceptibility genes: from gene mapping to gene function. Endocr Rev. 2003;24:694–717.

[25] Antonelli A, Ferrari SM, Frascerra S, Pupilli C, Mancusi C, Metelli MR, et al. CXCL9 and CXCL11 chemokines modulation by peroxisome proliferator-activated receptor-alpha agonists secretion in Graves' and normal thyrocytes. J Clin Endocrinol Metab 2010;95:413–420.

[26] Antonelli A, Fallahi P, Ferrari SM, Pupilli C, d'Annunzio G, Lorini R, et al. Serum Th1 (CXCL10) and Th2 (CCL2) chemokine levels in children with newly diagnosed Type 1 diabetes: a longitudinal study. Diabet Med 2008;25:1349–1353.

[27] Zignego AL. Enhanced TH1 cytokine production in hepatitis C virus-infected patients with mixed cryoglobulinemia: understanding the pathological issues. J Hepatol 2004;41:1045–1049.

[28] Antonelli A, Ferri C, Fallahi P, Ferrari SM, Frascerra S, Sebastiani M, et al. High values of CXCL10 serum levels in patients with hepatitis C associated mixed cryoglobulinemia in presence or absence of autoimmune thyroiditis. Cytokine 2008;42:137–143.

[29] Antonelli A, Fazzi P, Fallahi P, Ferrari SM, Ferrannini E. Prevalence of hypothyroidism and Graves disease in sarcoidosis. Chest 2006;130:526-532.

[30] Annunziato F, Cosmi L, Liotta F, Maggi E, Romagnani S. Human Th1 dichotomy: origin, phenotype and biologic activities. Immunology 2014 Oct 5. doi: 10.1111/imm.12399.

Table 1. Thyroid status of control subjects and patients with thyroditis.

	Controls	**AT**	**MNG**	***P***
N	1023	3069	1023	
Age (years)	53 ± 15	54 ± 16	54 ± 13	ns
Gender (% M/F)	27/73	27/73	27/73	ns
Thyroid volume	10 ± 3	9 ± 7	15 ± 9*°	0.007
Hypoechoic (%)	0	71	0	0.0001
Hypervascularity (%)	0	27	0	0.0001
TSH (μIU/mL)	1.5 ± 0.7	3.4 ± 4.7°§	1.0 ± 0.6	0.0006
AbTPO (IU/mL)	9 ± 6	367 ± 302°^	8 ± 9	0.0001
AbTg (IU/mL)	11 ± 10	189± 419°^	17 ± 19	0.0001
AbTPO positivity (%)	0	81	0	0.0001
AbTg positivity (%)	0	63	0	0.0001
Hypothyroidism				
Serum TSH > 3.5 μIU/mL (%)	0	26	0	0.001

Antithyroperoxidase antibody = AbTPO
Antithyroglobulin antibody = AbTg
Thyroid-stimulating hormone = TSH
$P < 0.005$ MNG vs. Controls = *
$P < 0.005$ MNG vs. AT = °
$P < 0.01$ TH vs. Controls = § or MNG < 0.01^

Table 2. Distribution of autoimmune diseases in AT patients, MNG and controls.

	Controls **n = 1023**	**AT** **n = 3069**	**MNG** **n = 1023**	***P*** **$\chi 2$**
Diabetes (type 1)	2	31	0	0.0003
Addison disease	0	7	0	0.0967
Chronic autoimmune gastritis	6	87	9	< 0.0001
Celiac disease	2	39	3	0.0005
Crohn disease	1	12	1	0.1446
Ulcerative colitis	1	17	2	0.0688
Vitiligo	5	83	2	< 0.0001
Alopecia	1	16	0	0.0148
Psoriasis	2	12	3	0.6237
Psoriatic arthritis	2	18	0	0.0180
Myasthenia gravis	0	3	0	0.3677
Polymyalgia rheumatica	3	44	5	0.0012
Polymyositisy/dermatomyositis	0	5	0	0.1886
Primary biliary cirrhosis	0	4	1	0.5131
Chronic autoimmune hepatitis	0	3	0	0.3675
Rheumatoid arthritis	7	74	5	< 0.0001
Systemic sclerosis (scleroderma)	0	16	0	0.0047
Sjogren disease	2	27	0	0.0001
Systemic lupus erythematosus	1	25	0	0.0008
Sarcoidosis	2	19	0	0.0133
HCV-related cryoglobulinemia	0	17	0	0.0034
Not–HCV-related cryoglobulinemia	0	2	0	0.5133
Glomerulonephritis Primary IgA	0	1	0	0.7165
Multiple sclerosis	3	27	2	0.0179
Uveitis (iridocyclitis)	2	9	4	0.7158
Wegener granulomatosis	0	1	0	0.7165
Total	40 (3.9%)	599 (19.5%)	37 (3.6%)	< 0.0001

Table 3. Patients with 3 associated autoimmune disorders in AT, MNG and controls.

	Controls **n = 1023**	**AT** **n = 3069**	**MNG** **n = 1023**	***P*** **$\chi 2$**
AT+CAG+Vit	0	12	0	0.0181
AT+CAG+Polym	0	5	0	ns
AT+CAG+Alo	0	2	0	ns
AT+CAG+T1D	0	2	0	ns
AT+CAG+SLE	0	1	0	ns
AT+CAG+Sarc	0	1	0	ns
AT+CAG+SSc	0	1	0	ns
AT+CAG+Sjog	0	1	0	ns
AT+Vit+Sjog	0	1	0	ns
AT+Vit+Polym	0	2	0	ns
AT+T1D+CelDis	0	2	0	ns
AT+RA+Vit	0	2	0	ns
AT+Sarc+Vit	0	1	0	ns
AT+Polym+UlcCol	0	1	0	ns
AT+Crohn+Vit	0	1	0	ns
AT+Sarc+Vit	0	1	0	ns
CAG+Vit+RA	1	0	0	ns
Total	1	36	0	< 0.0001

Alopecia (Alo); autoimmune thyroiditis = AT; celiac disease (CelDis); chronic autoimmune gastritis (CAG); Crohn disease (Crohn); polymyalgia rheumatica (Polym); rheumatoid arthritis (RA); sarcoidosis (sarc); sjögren's syndrome (Sjog); systemic lupus erythematosus (SLE); systemic sclerosis (SSc); type 1 diabetes (T1D); ulcerative colitis (UlcCol); vitiligo (Vit).