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Immune Associations in Hashimoto's Thyroiditis and Related Disorders

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Abstract

Material and method a) Diagnostic: A. Diagnostic of thyroid immune disease: ATPO and ATG investigation was considered as necessary and were correlated with ultrasound. B. Diagnostic of immune disease. The diagnostic was based on classical guides for every disease. 2. Patients: A. ?Classical? Hashimoto thyroiditis (hyper-ATPO-emia, HT) = 1276, B. thyroiditis with isolated hyper-ATG-emia, with normal ATPO (T-ATG) = 85, C. thyroiditis ?sero-negative? (normal ATPO and ATG, pathology diagnosis) = 9, D. idiopathic myxedema (hypothyroidism, no A,B,C) = 76; E. control = 1216 (no antibodies, when hypothyroidism, iatrogenic). b) Statistical analysis: ?2 test for comparing patients data with control data and z-test for comparing proportions. Results a) Immune association â??" in total: in HT = 237 (18.57

Index terms—

1 Introduction a) About organ specific vs systemic immune disorders

mmune/Autoimmune thyroiditis is considered as a limited disease, extended only to one organ -the thyroid. There are many organ limited immune disease, named as "organ specific". On the other hand, there are immune diseases expanded to the whole body; they are called "systemic" immune diseases.

The day to day practice showed that it is possible that one organ specific disease could be associated with another organ specific disease, or a systemic immune disease could be associated with another one, or with a more organ specific disease. In this paper we will present our experience based on over 40 years of observations (DP) on our patients with immune diseases, related to immune thyroiditis.

Based on "immune network" of Jerne (1985) (Nobel Price, 1984), we suggest that there is no organ specific, nor a systemic immune disease, but, instead, the entire clinical context is an "immune network" disruption.

Immune thyroiditis is characterized by inflammation of the thyroid, associated with specific immune mechanisms. Defining thyroiditis, the nosological Hashimoto thyroiditis has undergone a historical process.

Originally, Hakaru Hashimoto (1881-1934) described in 1912 (Hashimoto, 1912) a form of thyroid (D D D D) F roidism, that time called "myxedema" or "Ord's thyroiditis" [named from **??**illiam Miller Ord (1834 **??**1902) which described the atrophy of the thyroid with thyroid inflammation in 1877].

Subsequently, the pathogenesis of thyroid lesion was recognized as immunological and thus was named "lymphocytic", "chronic", and/or "autoimmune". Under clinical spectrum has been observed that patients with thyroiditis can be normothyroid (euthyroidism), not necessarily hypothyroid as originally Hashimoto described.

Investigating the pathogenesis of this disease, it has been observed that it is caused by an antibody called "antimicrosomal" because affected some thyreocyte cellular organelles, i.e. microsomes. After "antimicrosomal" antibody was discovered the antigen: thyroperoxydase. So, the name of antibody was changed from antimicrosomal to "antithyroperoxydase" (ATPO), as is now in use. Then, in some atrophic Ord's thyroiditis patients have been discovered the same antibodies.

In that moment, become obvious that the volume of thyroid is not essential in defining the disease; it is essential the immune process, which could lead, in evolution, to thyromegaly or to thyromicria even to atrophy.

So, Hashimoto's thyroiditis become that thyroiditis in which the pathogenesis was related to antithyroperoxydase antibody. It is a lymphocytic chronic inflammation of the thyroid, characterized by a specific immune mechanism, named antibody dependent cellular cytotoxicity (ADCC) (Rebuffat, 2008). In defining the disease, the thyroid size (bigger, as in Hashimoto's description or atrophic, as in Ord's description) has no importance, as the disease was defined by a pathogenetic mechanism.

Morevoer, thyroiditis classification shold not be depending on thyroid functionality. There are patients with the same pathogeny but with different thyroid function, either hyperthyroidism, or hypothyroidism. Moreover, most patients are euthyroid. Some researchers and authors (see, for example, Clerc, 2009) make inadequate distinction between "Hashimoto thyroiditis" (thyroiditis with "goiter", i.e. thyromegaly) and "chronic lymphocytic thyroiditis" (thyroiditis without "goiter"). This distinction is not based on a proper understanding of the pathogenesis of thyroiditis due to phenomena associated with ATPO, but is based on clinical grounds. These data do not have any impact on pathogenesis, which is the one which should define a nosological status.

The existence of an immunological mechanism strictly individualized makes without meaning the broader term "immune disease / autoimmune thyroid disease". In this broader context, some believe that Graves-Basedow disease, Hashimoto's thyroiditis, postpartum thyroiditis or silent forms of immune thyroid disease is a single disease or a continuous spectrum of disease (see **??**rifanescu, 2008).

Instead of viewing one immune disease, different multiple antibodies, and different multiple immune reactions should lead to consider the assertion "one mechanism -a disease" (Peretianu, 2012). In addition, other diseases have other immune mechanisms, and they are identified and clearly specified **??**Ganesh, 2007).

In chronic lymphocytic thyroiditis (considered as Hashimoto's thyroiditis), the presence of other antibodies (along ATPO), such as antithyroglobuline (ATG), lead to new nosological and taxonomical problems. As long as ATG are directed to another antigen and as long as the immune reaction is different (not ADCC, but, mostly, CDCC-complement dependent cellular cytotoxicity) (Ronco, 2009), adopting the concept "a mechanism -a disease", become that the ATG thyroiditis is another disease. If we accept that concept, we should named Hashimoto thyroiditis that immune disease based on ATPO mechanisms and related to ADCC mechanism.

Another problem occurs when thyroiditis has no antibodies; the condition could be named "seronegative" **??**Spina, 1990). The diagnosis was strictly pathologically and in serum were not observed any type of known antithyroid antibody. By adopting the concept of "an autoimmune thyroid mechanism -one thyroid immune disease", we could opbserved that "seronegative" thyroiditis could not be Hashimoto's thyroiditis. In the future, it will become another form of thyroiditis, when the antibodies and the antigens involved will be discovered.

Another condition related to immune thyroid diseases is that in which there is hypothyroidism, and ultrasound appearance, usually with thyromicria, but with no ATPO or no ATG. Since the patient do not performed a thyroid punction for a pathological exam, the condition should be named as "idiopathic myxedema".

Therefore, we analyze in this paper 4 immune thyroid conditions: thyroiditis due to ATPO (so called classical Hashimoto's thyroiditis), thyroiditis without ATPO but with high level of AGT (we named this condition ATG-thyroiditis), idiopathic myxedema (non induced hypothyroidism without ATPO and without ATG), and "seronegative thryroiditis" (thyroiditis on pathology but without any antithyroid antibody). The thyroid volume was: normal: 62.87 %, small (thyromicria or atrophy): 5.8%, high (thyromegaly): 31.33%. Patients with thyroid nodules: 6.50%. 2. Patients with hyper/high antithyroglobuline antibodies and with normal level of ATPO (hyper-ATG-emia thyroiditis): total: 85; women: 80, men: 5 (6.25%). Median age: 51 years. The ratio of men was similar to that in "classical" thyroiditis (p = 0.93, z = -0.08).

2 II.

3 Material and Method

There function was: euthyroidism: 62.55%, significative more that in hyper-ATPO-emia (p = 0.001, z = -3.24), hypothyroidism: 24.71%, significative less that in "classical" thyroiditis (p = 0.002, z = 3.08), hyperthyroidism: 12.94%, no differences between HT vs TATG (p = 0.76, z = 0.29).

The thyroid volume was: normal: 67.85%, similar in both TH & TATG (p = 0.35, z = -0.9); high (thyromegaly): 29.45%, similar in both TH & TATG (p = 0.71, z = 0.36); small (thyromicria): 2.70% (2 times lower than in hyper-ATPO-emia; p « 0.001, z = 5.57).

Patients with thyroid nodule: 18.95%, 3.5 times more as in hyper-ATPO-emia (p « 0.001, z = 8.56). Statistical analysis for our discrete data was performed with ? 2 test (usually for 2 rows and 2 columns). For percentage differences was used z-test.

4 III.

5 Results and Discusions a) In patients with hyper ATPO thyroiditis (Hashimoto's thyroiditis)

Another non-thyroid immune disease (or association which could have an immune/autoimmune substrate or mechanism) was registered in 237 patients (18.57%): 224 women and 13 men (5.49%).

The prevalence of men with thyroiditis was not different compared with the prevalence of men with an immune association and thyroiditis (5.49 vs 5.41%) [p = 0.07, z = -0.03]. That suggests that the immune association was not characterized especially for women. When appeared, thyroiditis is the same accompanied by an immune association irrespective of sex.

In the control group, an immune disease was registered in only 107 patients (8.80%). These ratios (18.57% vs 8.80%) lead to a very high statistical significance [p « 0.0001, ? 2 **??**> 24]. With other words: Hashimoto's thyroiditis associate more probable another nonthyroid immune disease than controls.

All the clinical situations were tabulated (table 2). * ! By listing the association at two or more clinical situations, the number of total cases is apparently higher than the number of patients ! ** see also Rovensky, 2010

Association of Hashimoto's thyroiditis with vitiligo: Vitiligo was observed in 37 patients (prevalence = 2.90%), 3 times higher than in controls (no = 11), with an increased significance (? 2 = 11.48; p = 0.0003), showing that vitiligo is very specific to thyroiditis. If added the patients from ATG-thyroiditis and idiopatic myxedema (see table 3 and table 4), vitiligo could be considered observed in 40 patients (prevalence in all thyroid immune disorders = 2.77%).

All our patients with thyroiditis-vitiligo associations were women. In the control group were 2 men with vitiligo (W:M ratio 5.5:1). Usually, in general population vitiligo is a women disease but only with 1.8 ratio (Schallreuter, 1994).Thus, vitiligo and thyroiditis was very specific to women. Thyroid function of our patients with thyroiditis and vitiligo was: euthyroidism: 15 (40.54%); hypothyroidism: 14 (37,84%); hyperthyroidism: 8 (21.62%). The general ratio of thyroid function in all patients (44.71%, 41.35%, respectively 13.94%) is slightly respected also in vitiligo patients, with an insignificant small amount of hyperthyroidism (z = -1.3; p = 0.18), suggesting that thyroid function did not influence the appearance of vitiligo in thyroiditis.

Concerning the apperance, 2 women presented very widespread vitiligo. Both cases were euthyroid. One the other hand, one woman from control group had the same. Moreover, one man from the control group had vitiligo, widespread only to penis.

Association of Hashimoto's thyroiditis with dermatitis: Allergic dermatitis (presented as chronic rush, eczema, prurigo, papules), sole (only with thyroiditis) or with other more complex associations (see table 2) is very frequent in our patients (no = 35; prevalence 2.74%). In control group we registered only 8 patients. The difference was very significant (? 2 = 15.96; p = 0.0001). Therefore, dermatitis should be considered as a clinical condition very associative with thyroiditis. If added the 4 patients with only hyper-ATG thyroiditis and 1 in idiopathic myxedema (see below), the prevalence of this condition in thyroid immune disorders could be closer to that observed in vitiligo (total prevalence = 2.70%).

Concerning sex ratio, the association thyroiditisdermatitis in our patients was over 6 times more in women than it was usualy described for dermatitis (W:M ratio 2 :1) (Peiser, 2012), since only 2 men were registered (W:M ratio 17.5 : 1).

The thyroid function of our patients with thyroiditis-dermatitis association was: euthyroidism: 43%; hypothyroidism: 43%; hyperthyroidism: 14%. This ratio fit the general thyroiditis functional ratio, suggesting that dermatitis could appered with any thyroid function. As unusualy appearance, one man presented association thyroiditis-dermatitis with high double stranded DNA antibodies.

Association of Hashimoto's thyroiditis with drug allergy: In our patients, we observed very frequently allergy to different drugs/medications (no = 27; prevalence 2.12%). In control group there were only 10 patients. This fact showed that drug allergy is very specific to Hashimoto's thyroiditis (? 2 = 7.12; p = 0.0076).

Allergy to penicillin is quite frequent (7 patients), being most registered antibiotic. Other antibiotics with allergy are: oxacillin, cefuroxime, and sulfamides.

Sometimes, severe forms of allergy were observed: anaphylactic shock to xyline/lidocaine and/or with Quincke edema (4 patients, table 2) (see also one patient with Quincke syndrome in only hyper-ATG thyroiditis -table 3).

An interesting drug allergy was observed in 3 patients with thyroiditis (ATPO increased) and Graves-Basedow (TRAB increased) associations in which per orem antithyroidian drug (methimazole, especially) triggered some forms of allergies.

Association of Hashimoto's thyroiditis with precocious menopause, probably due to immune ovaritis: We observed 16 women with precocious menopause (under 35 years). (prevalence = 1.25%). The prevalence of this condition in control group was much lower (no = 4), suggesting that precocious menopause could be considered as a clinical conditions very associative to thyroiditis (? 2 = 6.69; p = 0.0097). An additional patient with idiopatic myxedema was also observed (table 4).

As appearance, in one case, the menopause appeared at 15 years old ! Association of Hashimoto's thyroiditis with diabetes mellitus type 1: Insulin dependent diabetes mellitus (IDDM) was observed in 15 patients (prevalence = 1.18%). However, in the control group, the prevalence of IDDM was 6 patients. These data suggest that IDDM

could be a significant association in our patients, but was NOT achieved the statistical significance (? 2 = 3.47; p = 0.06 -missing one patient).

As concerning the thyroid function, 5 patients were euthyroid (33.33%), 7 patients were hypothyroid (53.33% vs 41.35 in all patients), and 3 were hyperthyroid (20%). Association IDDM-thyroiditis had presented mainly as hypothyroidism (but not reaching statistical threshold, z = -0.936, p = 0.35).

Association of Hashimoto's thyroiditis with allergic rhinitis:We registered 13 patients, most of them associated also with other immune conditions (see table 2). In control group was observed only 2 patients. Therefore, allergic rhinitis appeared as very associative with Hashimoto's thyroiditis (? 2 = 7. 6; p = 0.0059).

Three patients had both allergic rhinitis and bronchic asthma. 8 patients were euthyroid and 5 patients were hypothyroid.

Association of Hashimoto's thyroiditis with Biermer's pernicious anemia: Biermer's anemia was observed in 12 patients with thyroiditis, and with other clinical situations (see table 2). In control group we observed 2 patients with this disease. These data suggest that Biermer's pernicious anemia is a clinical condition very associative with thyroiditis (? 2 = 6.71; p = 0.0096).

As concerned the thyroid function, 6 patients were hypothyroid, 5 pateints were euthyroid and 1 was hyperthyroid. This specific association presented also with increased hypothyroid apperance (50% vs 41.35% in all patients).

Association of Hashimoto's thyroiditis with systemic lupus erythematosus, other major collagenosis and vasculitis: 12 patients could be viewed from major 2), most of them presenting multiple and unusual association.(D D D D) F collagenosis point of view (see table

One particular case, woman, had cerebral vasculitis (with changes in behaviour, with initiating a childish spelling), with Sneddon syndrome, pulmonary fibrosis, cryoglobulinemia, C hepatitis and sicca syndrome. Thyroid function was normal. The onset was at 35 years with a neurological disorder due to cerebral vasculitis: a childish spelling. Corticoids were tried at onset, without effect. After 6 months, the treatment was changed: cyclosporine 250 mg/day was used, under creatinine control, because of the negative effect of the drug on kidney. After hepatitis C discovering, interferon and ribavirin were administrated. ATPO antibodies decreased less than 34 mu/ml after IFN. The patient is still on cyclosporine; stopping cyclosporine lead to cerebral vasculitis with childish spelling behaviour.

Another woman presented Sharp syndrome, with multiple associations, including repetitive zona zoster, allergies to drugs, and repetitive alopecia areata. Thyroid function was normal. Thyroiditis was diagnosed at 21 years old. Dyspepsia apperared at 30 years. Sharp diseases appeared after menopause, at 48 years old. After that, 3 episodes of repetitive zona were registred. At 50 years was discovered thrombocytosis and the first alopecia episode appeared. The patient was (and is) in euthyroidism. When polyarthitis, dyspepsia, drug allergy and alopecia area symptoms appeared, was used only symptomatic treatment with NSAID, antiallergics, and dermatological topics.

Even there were a lot of patients with major vasculitis, these conditions did not lead to statistical significance, because in the control group we registered also a lot of patient (no = 8) with the same and other interesting immune disorders and associations (see table 2) (? 2 = 0.62; p = 0.43).

Association of Hashimoto's thyroiditis with immune enteric disease: Immune enteritis, in different clinical forms, either as celiac syndrome or as simple dyspepsia without obvious cause, was observed in 10 patients (see table 2). In the control group were observed 2 patients with enteric diseases. Therefore, enteric diseases was a close associtiion with thyroiditis (? 2 = 4.98; p = 0.025).

All our patients with thyroiditis-enteritis association were women. All, except one, were euthyroid. Therefore, we had not the possibility to search if the enteral disease diminished absorption of thyroxin, as others point out (Centanni, 2012). One patient was hyperthyroid, but not associated with Graves-Basedow disease (no TRAB).

In the control group was one man with Crohn disease, and one woman had ulcerative rectocolitis.

No patient with helicobacter pylori was registered as in other cases (Cammarota, 1997).

Association of Hashimoto's thyroiditis with bronchic asthma: We registered 9 patients with this clinical condition, mostly associated also with rhinitis and other conditions (see table 2). Our patients presented several crisis linked on exposure to their specific allergens (pollen, dust, dog or cat fur).

However, the disease was with the same prevalence in the control group (no = 10). Therefore, in our patient, asthma is NOT a condition associated preferentially with thyroiditis (? 2 = 0.73; p = 0.12). Even added the patients with only hyper-ATG and asthma (no = 2) (table 3), the statistics did not change.

Association of Hashimoto's thyroiditis with rheumatoid arthritis: We registered 8 patients with this association (prevalence: 0.63%). However, the prevalence among control group was higher (no = 20). That fact suggests that rheumatoid arthritis is not a specific association for thyroiditis. On the contrary: if a patient has rheumatoid arthritis, she/he could be protected against Hashimoto's thyroiditis (? 2 = 5.81; p = 0.01). Even we add the 4 patients from hyperTAGemia thyroiditis, "seronegative thryroiditis" and idiopathic myxedema to increase the prevalence of rheumatoid arthritis in thyroiditis (all related diseases), the number did not reverse the data. Therefore, our data are contrary to other authors who said that thyroiditisarthitis was very prevalent (Boelaert, 2010).

Association of Hashimoto's thyroiditis with alopecia areata: Alopecia areata, either localized (strictly areata)

or universalis, was registered in 8 patients, including a woman with alopecia totalis. One 16 old year man had only eyelashes alopecia.

In our patients, alopecia and thyroiditis association have a particularity: while the prevalence of alopecia in the general population is similar to equality in both sexes (1.15 females: 1 male) (Seyrafi, 2005), alopecia from thyroiditis is clearly in favour of women (ratio 7:1).

However, because alopecia in control group was registered in 2 patients, the significance of the association was borderline (? $2 = 3.33$; $p = 0.06$), missing 1 case.

Association of Hashimoto's thyroiditis with repetitive zona zoster: We registered 8 patients with this clinical condition. In the control group was 3 patients with zona zoster, but only one had repetitive zona. If we consider the repetitive aspect of zona, therefore, this clinical condition is highly associative with thyroiditis (? $2 = 5.13$; $p = 0.023$).

Repetitive zona zoster could be considered as an immunodeficient condition, and was described in association with a multitude of autoimmune disorders (O'Connor, 2013). Usually, the disease appear in older people. In our patients, the conditions was registred even at 26 year old (average age of zona onset in our patients was 55.62 y; SD 16.7).

Association of Hashimoto's thyroiditis with thrombophilia and the deficit of protein S: We registered 7 patients with these clinical conditions (see table 2). All were women. Most of the clinical conditions were related to pregnancy, either antepartum, intrapartum or postpartum. In the control group were registered also 3 women with this clinical condition, 2 in relation with pregnancy, the other in relation with amiodarone administration. The statistical significance was not achieved (? $2 = 1.42$; $p = 0.23$).

None of our patients were on the two conditions known to favour thromboembolism (Wu, 2006): estroprogestative oral medication and surgical procedure (especially orthopedic).

Even the statistical difference was not achieved, our patient are different from the general population related to thromboembolism accidents. They were all women, and it was known that sex ratio on thromboembolism was equal among sexes (Moores, 2004).

Association of Hashimoto's thyroiditis with autoimmune hepatitis: Autoimmune hepatitis was observed in 5 patients with thyroiditis, 3 of them associated with lupus, rheumatoid arthitis and vitiligo (see table 2). In the control group we registered also 2 patients with autoimmune hepatitis, a man who associated also with Crohn disease and a woman with another association, porphyria cutanea tarda.

Therefore, there is NO significant increase of autoimmune hepatitis in thyroiditis (? $2 = 1.15$; $p = 0.28$). In the context of the fact that immune therapies were used for viral C hepatitis, we observed 6 patients with interferon therapy (Pegasus R , Pegintron R , plus ribavirin). In 2 cases ATPO decreased, in 2 cases ATPO increased and in 2 cases ATPO behave undulatorious.

Association of Hashimoto's thyroiditis with multiple sclerosis: This clinical condition was registered in 4 patients, all women and all with other associations (see table 2). One patient in the control group had central demyelinisation. Therefore the association of thyroiditis with multiple sclerosis could be considered as a convincing association, even it was NOT reached the statistical significance (? $2 = 1.66$; $p=0.197$).

Association of Hashimoto's thyroiditis with otosclerosis: In our thyroiditis patients, we found 4 patients, all women. In control group there were 2 patients (see table 2). No statistical significance could be registred (? $2 = 0.58$; $p = 0.44$). If added the 3 patients with otosclerosis and hyper-ATG-emia thyroiditis (see below), the significance of this association did not change (? $2 = 2.26$; $p = 0.13$).

As in other clinical associations (see above), otosclerosis in our patients has a particularity: much more in women, since usually, the sex prevalence of otosclerosis is 1 man vs 1.15 women (Perez, 2009).

Association of Hashimoto's thyroiditis with corticosuprarenal insufficiency: This clinical situation was registered in 4 patients, as Schmidt syndrome along with other immune associations (see table 2). Corticosuprarenal insufficiency-thyroiditis association is quite strong, since in the control group was no such a patient (? $2 = 3.82$; $p=0.05$).

Three patients were hypothyroid (75%) and one was euthyroid. An additional hypothyroid case was registred in idiopatic myxedema.

Association of Hashimoto's thyroiditis with hematological proliferation diseases, including lymphomas: Hodgkinian and nonhodgkinian lymphomas occur in 3 patients with thyroiditis. The association appears to be weak since in the control group we registered 1 patient (? $2 = 0.91$; $p = 0.34$). All lymphomas were extrathyroid.

If we add more 2 patients with thyroiditis associated with multiple myeloma (1 case) and benign monoclonal gammapathy (1 case), then the mathematical test is changed (? $2 = 2.48$; $p = 0.11$), but not reaching the statistical significance.

6 Association of Hashimoto's thyroiditis with other clinical situations with an immune/autoimmune condition:

Other clinical immune associations with thyroiditis with only 2 patients or 1 patient were registered (see table 2). They are interesting only from description point of view. Obviously, no one have any statistical relevance.

Moreover, in the control group were registered more patients with other immune disordes. For exemple, in the

control group we registred 4 patients with ankylosing spondilytis vs. 1 in thyroiditis, fact which are contrary to other studies (e.g. Peluso, 2011).

Considering hypophysitis diagnosed as such (no = 2), we observed in our patients 9 additional patients with hypo-IGF-1, three with exophthalmia, hyperthyroidism and Graves-Basedow association, and one with diplopia and hypothyroidism. A pituitary lesion was not diagnosed in these patients.

On the other hand, we registered 5 patients with high levels IGF-1, without acromegaly, 4 of them associated exophthalmia, hyperthyroidism and Graves-Basedow association. No speculation or conclusion can be done.

Only one vs. multiple associations: We observed 168 patients with only one immune disorder associated with Hashimoto's thyroiditis. The prevalence was 70.89%. The other patients (no = 69, prevalence = 29.11%) presented multiple associations. Some of them were registered with 5 or 6 associations.

7 (D D D D) F

Some interesting association to Hashimoto's thyroiditis could be described (see also table 2): ? Cerebral vasculitis with Sneddon syndrome, pulmonary fibrosis, cryoglobulinemia, C hepatitis (treated with IFN), and sicca syndrome in a woman (see above). ? Sharp disease with repetitive alopecia areata, dyspepsia, repetitive zona zoster, allergy to betablokers and thrombocytosis in a women (see above).

8 b) Immune associations in only hyper ATG thyroiditis

Another non-thyroid immune disease (or association which could have an immune/autoimmune substrate) was registered in 23 patients from 85 (27.06%). All the patients were women.

The prevalence of this association compared with that in "classical" thyroiditis (with high ATPO) (18.50%) was higher. Statistical significance was at border (p = 0.054, z = -1.93). However, the clinical significance could be considered as hidden, since in this form of thyroiditis there were more patients with euthyroidism than hypothyroidism (see above, table 1).

Allergic rhinitis (1) Psoriasis (1) Otosclerosis (3) * ! By listing all the associations, from both/many points of view, the number of cases is (apparent) bigger than that of patients ! The most frequent associations were with: dermatitis (4 patients), otosclerosis (3 patients), vitiligo (2 patients), and bronchial asthma (2 patients).

From these data, we could point out that this thyroid immune condition (i.e. hyper-thyroglobuline thyroiditis) was highly associated with otosclerosis (? 2 = 23.50; p « 0.0001) and dermatitis (? 2 = 18.65; p « 0.0001) [compared with the control group]. Vitiligo, bronchial asthma and drug allergy were associated with a nonstatistical threshold (? 2 = 2.79; p = 0.09) [missing only one patient for attending the threshold of 0.05].

9 c) Immune associations in idiopathic myxedema

In idiopathic myxedema (no = 76), we registered 11 patients with a nonthyroid immune association; prevalence = 14.47%. The prevalence is lower than that observed in "classical" thyroiditis, and is between the prevalence of the control group. [1] [2] [3] [4] [5] [6] [7] [8] [9]

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Figure 1:

1

thyroiditis diagnostic. The cut-off was considered at 34/35 u/ml. We used usual laboratory commercial kits for both antibodies We used electochemi-

3. Idiopathic myxedema: total: 76; women: 67, men: 9 (13.43%), more that in the other thyroid disorders (p vs HT = 0.35, NS). Median age: 60 years. The function was 100% hypothyroidism.

Thyromicria: 13.04% was twice as in Hashimoto's thyroiditis.

4. Seronegative thyroiditis: total: 9; all women. Median age: 53 years. The thyroid function was: euthyroidism: 87.5%, hypothyroidism: 12.5%. All had thyroid nodules, for which they were punctioned. One patient associated also ultrasound hypoechoic pattern as in classical thyroiditis.

5. Control group was formed by patients who were investigated for a thyroid disorder. In this group most patients were with thyroid nodules (60.46%), either macro (>1 cm) or micro. Normal thyroid was registered in 22.29% patients. In this group, around 1 hogenic non-nodular homogenous/ inho-mogenous thyroid, as was observed in thyroiditis in 91.77%. In all these patients, the antibodies were normal: no high ATPO, no high ATG. Total: 1216; women: 1088, men: 128 (11.76%). Median age: 54 years. Their thyroid function was: euthyroidism: 92.26%, hypoth-yroidism: 2.72%, hyperthyroidism: 5.02%.

	Classic Hashimoto thyroiditis (hyperATPOemia)	Thyroiditis with only hyperATG-emia (normal ATPO)	Idiopathic myxedema (hypothyroidism, normal ATPO, normal ATG)	Sero negative thyroiditis (pathological diagnosis)	Control group
Number	1276	85	76	9	1216
Age Average	50.21	50.07	57.93	45.00	53.65

Figure 2: Table 1 :

2

Immune association in Hashimoto's thyroiditis	Immune disease in control group
Vitiligo without other associations (19)	Vitiligo without any other associations (10)
Vitiligo plus exophthalmia and Graves-Basedow disease (1)	Vitiligo plus rheumatoid arthritis (1)
Vitiligo plus Graves-Basedow (2)	
Vitiligo with immune hepatitis and hepatic cirrhosis (1)	
Vitiligo plus skin allergy (1)	
Vitiligo and acoustic neuroblastoma (1)	
Vitiligo plus alopecia areata (1)	
Vitiligo plus allergic rhinitis (1)	

Figure 3: Table 2 :

3

HyperATG thyroiditis (without hyper/high ATPO)	
Vitiligo without other association (1)	Rheumatoid arthritis with vitiligo (1)
Vitiligo plus rheumatoid arthritis (1)	Systemic lupus erythematosus, pulmonary fibrosis and celiac disease (1)
Dermatitis to cat fur (1)	Phospholipidic syndrome (1)
Dermatitis, eczema to nickel (1)	Celiac disease with systemic lupus erythematosus and pulmonary fibrosis (1)
Allergic dermatitis without other associations (2)	Neutropenia post blood (1)
Drug/Medication allergy (2), acetylsalicylic acid and nonspecified	Quincke edema to acetylsalicylic acid (1)
IDDM without other associations (1)	Multiple sclerosis (1)
Bronchial asthma without other associations (2)	Thrombocytemia

Figure 4: Table 3 :

4

Immune associated disease with idiopathic myxedema
Rheumatoid arthritis (2)
Systemic lupus erythematosus and C hepatitis (1)

Figure 5: Table 4 :

9 C) IMMUNE ASSOCIATIONS IN IDIOPATHIC MYXEDEMA

Vitiligo (1) Dermatitis (1) Bronchic asthma (2) Idiopathic neutropenia (1) Precocious menopause (probable due to immune ovaritis) (1) Biermer anemia (1) Schmidt syndrome (hypothyroidism with Addison disease), decreased IGF-1, ferriprive anemia by lack of Fe absorption (1) No specific conclusions could be done from these ases.

All the clinical situations were tabulated (table **??**) All the clinical situations were tabulated (table **??**)

.1 d) Seronegative thyroiditis

From 9 patients, only 1 woman presented an immune association: rheumatoid arthritis.

.2 IV. General Discussion and Conclusions

In the literature, there are many papers in which authors found thyroiditis in another specific immune disease: e.g.: Sjögren (Zeher, 2009), pemphigus (Pitoia, 2005), celiac disease (da Silva Koetze, 2006), rush (Zauli, 2001), dermatitis (Irani, 2012), alopecia areata (Seyrafi, 2005), vitiligo (Daneshpazhooh, 2006), ankylosing spondylitis (Peluso, 2011).

Moreover, the literature is full of isolated cases, in which multiple associations, including thyroiditis are presented, and described as "unusual". Usually, the starting disease is not thyroid. Some of our current patients are also very interesting, and could be viewed like "spectacular", even they are simply a case of "immune network disruption".

We published also isolated patients with immune associations, including a thyroid one, e.g.: Peretianu, 2006, concerning Graves-Basedow-systemic lupus erythematosus-psoriasis-vitiligo-alopecia areata, all in 2 patients; Peretianu, 1989, thyroiditis-rheumatoid arthritis-hypogonadism; Peretianu, 1990, Graves-Base dow diseases with ulcerative recto-colitis.

Much rare, researchers analyzes the patients starting from the thyroid point of view (like eg, Boelaert, 2010, Centanni, 2012), searching the immune conditions associated with a known thyroid disorders. For exemple, Boelaert found a prevalence of 14.3% immune disorders in thyroiditis and 9.67% in Graves-Basedow disease (Boelaert, 2010). Centanni found a prevalence of 16.2% immune disorders in thyroiditis (Centanni, 2012).

Our data showed slightly higher values on the prevalence thyroidis-immune association: 18.57% for classical (hyperATPO) thyroiditis, or 27.06% for hyper thyroglobuline thyroiditis (without hyper-ATPO). If we considered all our patients, with "classical" thyroiditis, ATG-thyroiditis, seronegative thyroiditis and idiopathic myxedema, the prevalence of an immune (auimmune) disease could be registred in 18.81% patients.

The differences on specific association prevalence between authors could have as origin bias reasons. For example, Centanni, could be bias on gastric and intestinal associations, since his group was involved in searching how thyroxin is absorbed (Centanni, 2012). That could led make more easyly to a diagnosis of gastric atrophy (with Biermer's anemia) or/and celiac disease (in his study 34.8%, respectively, 11.1%). Boelaert (2010) could be bias on rheumatoid arthritis, maybe a disease widespread in England.

We tried to bring a new approach; we analysed the immune associations comparing with a group of patients without an immune thyroid disease. From this point of view, we showed that it is not important the number of cases registered but the comparison with the same diagnosis in the "control" population.

From this point of view, in our patients, the most associative (and significant) immune disorders with thyroiditis were (in this order): vitiligo, dermatitis, drug allergies, precocious menopause (immune ovaritis), allergic rhinitis, Biermer's anemia, repetitive zona zoster, and corticosuprarenal insufficiency. Borderline could be considered multiple sclerosis, alopecia areata, IDDM, and thrombophilia.

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