UNIVERSITY OF MEDICINE AND PHARMACY
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DOCTORAL THESIS

HLA PROFILE OF PATIENTS WITH AUTOIMMUNE MARKERS AND ADVERSE REACTIONS OF HYPERSENSITIVITY TO NONSTEROIDAL ANTI-INFLAMMATORY DRUGS

-SUMMARY-

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General Data

I. Autoreactive urticaria

Chronic urticaria is characterized by local or disseminated plaque rash whose duration exceeds 6 weeks. Some of the patients with chronic idiopathic urticaria (30-50%) suffer in fact from chronic autoimmune urticaria [Greaves, 2003], due to IgG antibodies to the IgE receptor of high affinity, FceRI or, less frequently, anti-IgE antibodies. This type of autoimmune urticaria, also called autoimmune mastocytosis [Greaves, 1995] can have a more severe evolution. Although the treatment is similar to that of chronic idiopathic urticaria, the therapeutic answer to H₁ antihistaminic medication is slow [Greaves, 2003], which is also confirmed by my personal experience. Detecting patients with chronic autoimmune urticaria through autologous serum skin test (ASST) can be of significance in this context [Sabroe et al, 2002]. The prevalence of autoimmune urticaria in adults is around 40%, whereas in children, it is 30% [Brunetti L et al, 2004].

II. Autoimmune thyroiditis

Autoimmune thyroiditis involves the occurrence of an immune answer against self-antigens. In the case of autoimmune thyroiditis, the main targets are: thyroglobulin (TG), thyroid peroxidase (TPO) and thyrotropin (TSH) receptor. In Hashimoto's thyroiditis, the signs and symptoms vary throughout the natural evolution of the disease, the autoimmune presence being initially accompanied by a normal thyroid function (TSH, T₄ and T₃ within normal limits).

From among detected autoantibodies, the most important are thyroid peroxidase antibodies and thyroglobulin antibodies. They are detected in more than 80% of the persons diagnosed with Hashimoto's thyroiditis. The capacity of TPO antibodies to fix the complement (the classic path) can be one of the pathways responsible with the thyroid cell destruction [Stassi G, 2002].

The results of hormone therapy in the case of the association of autoimmune thyroiditis with chronic urticaria are contradictory [Kandeel AA, 2001]. Patients with chronic autoimmune urticaria suffer from an important decrease of the quality of life due to intensive pruritus, insomnia and skin lesions affecting their physical appearance. In certain situations, which are well-established, hormone therapy improves significantly the quality of patients’ life through more rapid urticaria remission [Shahid A., 2005].
III. **Hypersensitivity to non-steroidal anti-inflammatory drugs**

Used on a large scale especially for their anti-inflammatory action, NSAIDs are responsible with approximately 21-25% of adverse medication events. The first description of a hypersensitivity reaction to aspirin was noted by Hirschberg in 1902. Ever since, several types of NSAIDs hypersensitivity reactions have been noted. Hypersensitivity to aspirin or other NSAIDs is clinically manifest through a wide range of symptoms: from vasomotor rhinitis with profuse rhinorrhea, angioedema, generalized urticaria and asthma to larynx edema, bronchospasm, rash, hypotension and shock. Reports on the prevalence of hypersensitivity to aspirin in the general population locates it between 0.6% and 2.5% [Nizankowska-Mogilnicka E., 2007]. Cutaneous manifestations of NSAIDs hypersensitivity affect approximately 0.3% of the general population [Settipane RA., 1980], but the prevalence increases significantly in the case of patients with chronic urticaria [Erbagci Z., 2004].

Considering that patients with NSAIDs induced urticaria react mostly to COX1 inhibiting anti-inflammatory drugs, it was considered that the mechanism triggering this reaction is the same as in the case of asthma exacerbated by NSAID [Quiralte J, 2007]. Cyclooxygenase inhibition leads to the reduction of protective prostaglandins synthesis and the increase of inflammation mediators synthesis in cutaneous cells. Eicosanoids release after NSAID administration occurs in both clinical situations (asthma and urticaria) [Mastalerz L, 2004; Setkowicz M, 2009].

IV. **Genetic profile of patients with NSAID hypersensitivity and autoimmune markers**

Several researchers have provided evidence referring to the presence of certain human leukocyte antigens in patients with chronic urticaria. O'Donnell was among the first researchers who published data on the presence of certain genes in patients with chronic idiopathic urticaria. Starting from the existing data on the possible autoimmune etiology of chronic idiopathic urticaria through the presence of anti FceRI antibodies, he raised the suspicion of a potential genetic involvement located in MHC class II. He detected a higher frequency of DRB1*04 (DR4) associated with DQB1*0302 (DQ8) in patients with chronic idiopathic urticaria as compared to the control group [O’Donnell B.F., 1999].

It seems that there is an association between a certain HLA fenotype and Hashimoto's thyroiditis (HT) in various ethnic groups. Thus, the first studies conducted in Canada on Caucasian population (40 patients) emphasized the association between HLA DR5 and HT goiter form with a relative risk of 3.1 [Farid NR, 1981] and HLA DR3 and HT atrophic form, with a relative risk of 5.1 [Moens H., 1978]. In 2008 Zeitlin et al published an article revealing the existence of a strong association between autoimmune Hashimoto's thyroiditis and HLA DR4 [Zeitlin AA, 2008].
Kim et al suggest the existence of an association between a certain HLA class II genotype and NSAIDs-induced urticaria, which is proven by techniques of high resolution analysis. The frequency of HLA-DRB1*1302 and HLA-DQB1*0609 alleles in patients with NSAIDs-induced urticaria was significantly higher than in patients with aspirin-induced asthma or the control group (healthy patients) suggesting their importance as genetic determinants of the NSAIDs-induced urticaria phenotype [Kim SH, 2006].

As regards the association of between certain HLA class I alleles with chronic idiopathic urticaria in patients with NSAID hypersensitivity, Pacor published in 2006 a study which revealed that two HLA-Cw (HLA-Cw4 and HLACw7) alleles seem to be less frequent in AICU patients, whereas the presence of HLA-B44 was significant in the group of patients with chronic idiopathic urticaria which associates reactions of NSAID hypersensitivity [Pacor, 2006].

**Specific data**

**I. Objectives**

1. The first objective of this study was to bring information on the prevalence of autoreactive urticaria within chronic idiopathic urticaria and to assess its association with autoimmune thyroiditis, as well as the risk of the occurrence of hypersensitivity reactions to classical nonsteroidal anti-inflammatory drugs in the case of the association between the two pathologies, as compared to the group of patients who do not associate autoimmune markers.

2. The second objective was to analyze the potential association between a certain HLA profile and autoimmune urticaria associated with autoimmune thyroiditis in patients with a history of hypersensitivity to non steroidal anti-inflammatory drugs.

3. The third objective was to set the therapeutic safety profile of methylsulfonyl selective COX2 NSAIDs in patients with a history of hypersensitivity to classic nonsteroidal anti-inflammatory drugs, COX non-selective. Drug challenge tests were performed as a golden standard to etoricoxib.

4. The fourth objective was to establish the efficiency of pharmacological treatment associated with chronic autoimmune urticaria considering associated pathology.

**II. Materials and Methods**

The study was performed on a group of 238 patients with chronic idiopathic urticaria, who were referred to the Allergology Clinic of the hospital “Nicolae Malaxa” in Bucharest during one year. All the patients with chronic urticaria without an obvious cause, underwent the following tests: full blood count
(FBC), erythrocyte sedimentation rate (ESR), nasal and throat swabs, urine culture, stool microscopic examination, serology for B, C hepatitis and HIV (immunochromatography), anti-double-stranded DNA (dsDNA) (latex agglutination), C₃, C₄ and rheumatoid factor (immunonephelometry).

Once an obvious cause was excluded, the patients included in the study were assessed for autoreactivity using autologous serum skin test (ASST) in compliance with EAACI/GA2LEN task force consensus report [Konstantinou G. N., 2009]. For patients in both groups (the group with positive autologous serum skin test and the negative ASST), the levels of free thyroxine and thyroid-stimulating hormone were measured. The same method (chemiluminescence) was used to determine the thyroid peroxidase (ATPO) antibodies.

For the analysis of a potential association between a certain HLA profile and autoimmune urticaria associated with autoimmune thyroiditis in patients with a history of hypersensitivity to anti-inflammatory drugs, I monitored a group of 63 patients, selected from the first group diagnosed following investigations carried out in our clinic with chronic autoreactive urticaria associated with autoimmune thyroiditis. They were taken blood for HLA phenotype detection, made with the support of the histocompatibility laboratory of the National Blood Transfusion Institute “Prof. Dr. C. T. Nicolau”.

In order to set the therapeutic safety profile of methylsulfonyl selective COX₂ NSAIDs in patients with a history of reactions of hypersensitivity to classic nonsteroidal anti-inflammatory drugs, non-selective COX, I monitored a group of 118 patients, selected from all the patients included in the the first objective, with a personal history of hypersensitivity to nonsteroidal anti-inflammatory drugs. They were subjected to the drug challenge test, using the same nonsteroidal anti-inflammatory drug, selective COX₂ with methylsulfonyl structure (etoricoxib). The test was made in the clinic, with permanent monitoring of the patients, following the specific stages according to international protocols. The drug challenge tests were mono-blind placebo controlled.

In order to set the efficiency of the associated pharmacological treatment on chronic autoimmune urticaria with the associated pathology I monitored a group of 63 patients, selected from the first group following investigations made in our clinic on chronic autoreactive urticaria associated with autoimmune thyroiditis, whose urticaria activity score is higher than four points. This study was unfolded during three visits. On the first visit, after being grouped according to inclusion criteria, patients received H₁ antihistaminic medication in large doses, being reassessed after four weeks of treatment. On the second visit, patients were sub-grouped according to the associated pathologic function in two sub-groups (A and B) that followed different pharmacological treatments. Sub-group A (23 patients) containing patients who kept a urticaria activity score higher than three and who suffered from the thyroiditis (subclinical or clinic hypothyroidism) also received L-thyroxine, after being evaluated by the specialist endocrinology doctor.
Sub-group A was reassessed 4 weeks after the hormone treatment. Sub-group B (13 patients) consisted of patients who, on the second visit, had one point as urticaria activity score under treatment with large doses of H$_1$ antihistaminic drugs, but had various degrees of depression. The depression degree was established after psychological evaluation by a certified clinician psychologist. In setting the diagnosis, he used the depression symptoms questionnaire (validated for the Romanian population). They received associated treatment with mirtazapine and were re-assessed during the third visit after four weeks of treatment by applying similar assessment procedures (the urticaria activity score and the questionnaire on depression symptoms).

III. Results, debates, conclusions

III.1. Prevalence of autoreactive urticaria within chronic idiopathic urticaria

The group with autoreactive urticaria was represented by 133 patients (55.88%) of the patients with chronic idiopathic urticaria.

The average age of patients included in the study was 43.19 ± 15.4 (limits between 18 and 82 years of age), with net predominance of the women’s group (70.16%).

The average duration of evolution of urticaria was 30.35 ± 24.11 months, with significant variations, depending on the distinct age groups.

In respect of the number of patients divided on age groups, it was noted that most patients belonged to the age group 30-55 years. Practically, approximately half (51.68%) of all patients with ASST positive belong to this age group.

Conclusions:

- A relatively high percentage of patients with chronic idiopathic urticaria present a positive autologous serum skin test (approximately half of the cases). The ASST is currently considered the only *in vivo* test which assesses autoreactivity.
- Patients with autoimmune urticaria have a longer duration of disease evolution, and the response to conventional therapy is considerably slower.
- The vast majority of patients with autoimmune urticaria are women, possibly in the same context of women’s predisposition to develop autoimmune diseases.
III.2. Prevalence of autoimmune thyroiditis in patients with chronic autoreactive urticaria

The probability of coexistence of autoimmune thyroiditis and chronic urticaria was significantly higher in patients who associated a positive autologous serum skin test (63 patients representing 47.36% from all patients with ASST positive), as compared to those whose autologous serum skin test was negative (5 patients, namely 4.76% from all patients with ASST negative) [(a) Tudose AM, 2012].

Following free T₄ and TSH screening, the thyroid status was measured in all patients with ASST positive including those with high thyroid peroxidase antibodies. From among these, thirty four were diagnosed with Hashimoto's thyroiditis in euthyroid status (25.56%), twenty with sub-clinic hypothyroidism (15.03%). Nine of the patients (6.76%) had clinical hypothyroidism manifestations requiring a hormone supplement.

The prevalence of autoimmune thyroiditis in patients with chronic urticaria (the group of 238 patients) was 28.56%. In exchange, the prevalence among patients with autoreactive urticaria (positive autologous serum skin test) increases significantly, reaching the value of 47.36%. The study reveals a higher prevalence of autoimmune thyroiditis in the case of patients with positive autologous serum skin test as compared to that in patients with negative autologous serum skin test, suggesting a link between the two conditions.

Conclusions:

- The incidence of autoimmune thyroiditis is higher in patients with autoreactive urticaria (positive autologous serum skin test) as compared with patients with chronic urticaria with negative autologous serum skin test.
- The vast majority of patients with autoimmune thyroiditis have normal thyroid gland function.
- Thyroid screening is necessary in all the patients with chronic autoreactive urticaria.

III.3. Prevalence of NSAIDs hypersensitivity in patients with autoimmune urticaria and thyroiditis and the influence of autoimmunity markers on the risk of its occurrence.

In the group of patients with positive ASST (133 patients), there were 98 patients with a history of NSAIDs hypersensitivity, and in the group of patients with negative ASST (105 patients), twenty patients had a history of NSAIDs hypersensitivity. The percentage of patients with NSAID hypersensitivity in the group with positive ASST (73.68%) was similar to that of patients with positive ASST and high TPO antibodies (71.42%). In the case of patients with negative autologous serum skin test, the percentage of patients with NSAIDs hypersensitivity was significantly lower (19.04%). As regards the distribution of
cases on gender, following the same line, the frequency of hypersensitivity reactions to NSAIDs was higher in women as compared to men in all age groups. To conclude, the NSAIDs hypersensitivity presence is directly proportional to the presence of autoimmune markers.

The analysis of logistic regression, applied to the two groups (positive ASST and high TPO antibodies – group 1/negative ASST and normal TPO antibodies – group 2) reveals that, although patients with high TPO antibodies have a higher degree of occurrence of NSAIDs hypersensitivity, these auto antibodies have a very small influence on the occurrence of NSAIDs hypersensitivity. In exchange, the size that can influence the occurrence of NSAIDs hypersensitivity is the autologous serum skin test. The presence of a positive autologous serum skin test increases the likelihood of occurrence of NSAIDs hypersensitivity, whereas a negative autologous serum skin test decreases the likelihood of occurrence of NSAIDs hypersensitivity. Both models of logistic regression are statistically significant (p<0.0001).

**Conclusions:**

- Hypersensitivity to nonsteroidal anti-inflammatory drugs is more common in patients with autoimmune markers.
- Women are more prone to such reactions.
- It is necessary to impose precaution measures on the use of nonselective COX NSAIDs in patients with autoimmune markers.
- The presence of a positive autologous serum skin test increases the likelihood of NSAIDs hypersensitivity.

### III.4. HLA profile in patients with autoimmune markers and a history of NSAIDs hypersensitivity

The frequency of HLA-A2 was the highest among HLA-A, being comparable between the two groups (first group - positive ASST and high TPO antibodies with a history of NSAIDs hypersensitivity vs. second group - positive ASST and high TPO antibodies without a history of NSAIDs hypersensitivity) (31.46% vs. 36.67%). Higher frequencies of HLA-A occurrence for the first group compared with the second group were registered for HLA-A11 (13.48% vs. 3.33%) and HLA-A1 (12.36% vs. 6.66%).

For HLA-B, the highest frequency of occurrence in group one was for HLA-B35 (36.66%), followed by HLA-B18 (15.56%), HLA-B44 (6.66%) and HLA-B57 (5.55%) with significant difference between the two groups for HLA-B44 (6.66% group one vs. 0%) and HLA-B57 (5.55% vs. 2.77%).

For HLA-C the highest frequency for the occurrence of HLA-C7 was followed by HLA-C4 and HLA-C5. The two groups have frequencies similar to these genes, except for HLA-C5 which is not found in the group of patients without a history of hypersensitivity to nonsteroidal anti-inflammatory drugs.
For HLA-DR the highest frequency of occurrence was for HLA-DR\textsubscript{13} in group one (21.87% vs 13.04%). Although the predominance of HLA-DR\textsubscript{4} was described in patients with chronic urticaria, in my groups, its occurrence frequency did not reveal any significant variations (7.81% in group one vs 8.69% in the second group).

For HLA-DQ the highest occurrence frequency was for HLA-DQ\textsubscript{6}, but was similar in both groups. In my groups included in the study, HLA-DQ\textsubscript{5} was no found, a result which was similar to that of another study published in 2005 [Chen J, 2005]. The higher frequency of HLA-DQ\textsubscript{6} in the two groups with urticaria was also present in other studies published until now [Ye YM, 2008; Kim SH, 2005].

### III.5. The HLA influence on the risk of occurrence of NSAIDs hypersensitivity

After applying the logistic regression the genes: HLA-\textsubscript{A}1, HLA-\textsubscript{B}44, HLA-C\textsubscript{5}, HLA-DQ\textsubscript{8} and HLA-DR\textsubscript{4} taken together influence the occurrence of NSAIDs hypersensitivity (p = 0.0360). But a single gene does not keep a sufficient statistical significance. Practically, the risk of occurrence of the NSAIDs hypersensitivity seems to be rather determined by an association of genes out of which HLA-C\textsubscript{5} has a crucial role.

The highest statistical significance seems to be represented by the model without DR\textsubscript{4} and DQ\textsubscript{8} (p = 0.0083). Although there are several studies where the two HLA have a high frequency, the association represented by HLA-A\textsubscript{1}, HLA-B\textsubscript{44}, HLA-C\textsubscript{5} seems to influence significantly the occurrence of NSAIDs hypersensitivity in Romanian patients with autoimmune urticaria and thyroiditis.

The antigens with a higher occurrence frequency in the groups of my study comparable with the occurrence frequency in the control group were HLA-A\textsubscript{11}, HLA-B\textsubscript{57}, HLA-C\textsubscript{1}, HLA-C\textsubscript{3}, HLA-DR\textsubscript{13}, HLA-DR\textsubscript{16}.

The logistic regression in the case of binary variables cannot be applied when the number of occurrences of value 1 is smaller or equal to 5. In the present study, the presence of HLA-DR\textsubscript{16} and HLA-C\textsubscript{1} was less than five cases, therefore were excluded from the logistic regression analysis model.

I obtained the statistical significance, p<0.05, for the model where I studied the influence of HLA-A\textsubscript{11} gene in the group with the NSAIDs hypersensitivity + variable. Indirectly, the validity of this model where the role of HLA-A\textsubscript{11} was analyzed in the pathogenicity of chronic urticaria in patients with NSAIDs hypersensitivity was confirmed by lack of statistical significance of models where the HLA-A\textsubscript{11} gene was missing. In the case of the other models I did not obtained a statistical significance, but I consider that a CLINICAL significance can also be found in models whose variable is the dependence HLA-A\textsubscript{11} + HLA-C\textsubscript{3} + HLA-DR\textsubscript{13} (p = 0.0973), HLA-A\textsubscript{11} + HLA-B\textsubscript{57} (p = 0.0888), HLA-A\textsubscript{11} + HLA-C\textsubscript{3} (p = 0.0632) as well
as HLA-A11 + HLA-DR13 (p = 0.0923). It is possible for future studies with a larger group of patients to determine whether such genes have or have not a role in the pathogenicity of chronic urticaria with NSAIDs hypersensitivity.

Conclusions:

- HLA-A1, HLA-B44, HLA-C5, HLA-DQ8 and HLA-DR4 taken together influence the occurrence of NSAIDs hypersensitivity.
- Each HLA does not have, however, a sufficient statistical significance.
- The risk of NSAIDs hypersensitivity seems to be determined by a association of specific HLA.
- HLA-C5 has a crucial role.
- The combination represented by HLA-A1, HLA-B44, HLA-C5 influences significantly the occurrence of NSAIDs hypersensitivity in Romanian patients with autoimmune urticaria and thyroiditis.
- HLA-A11 influences the likelihood of NSAIDs hypersensitivity in Romanian patients with autoimmune urticaria and thyroiditis (p< 0.05).
- Clinical significance could also be found in other models with p<0.1, but these models have to be prove on a larger group of patients.

III.6. Frequency of hypersensitivity reactions depending on the NSAIDs type

Hypersensitivity reactions to NSAIDs have been reported frequently in patients included in the study. 118 patients, 49.57% (from all patients with chronic idiopathic urticaria - 238 cases) had a history of hypersensitivity to NSAIDs.

In the case of patients with chronic urticaria with positive ASST (133 subjects) I identified 98 subjects with a history of NSAIDs hypersensitivity (73.68%). From among these, 37 (37.75%) presented NSAIDs hypersensitivity at ibuprofen, 17 (17.34%) at diclofenac, 18 (18.36%) at ketoprofen and 26 (26.53%) at aspirin.

From among patients with negative ASST (105) I found 20 cases of NSAIDs hypersensitivity (19.04%) distributed as follows: 9 cases of NSAIDs hypersensitivity which involved ibuprofen (45%), 2 cases of NSAIDs hypersensitivity at diclofenac (10%), 3 cases at ketoprofen (15%) and 6 cases at aspirin (30%). In both groups, the highest percentage of patients with NSAIDs hypersensitivity was represented by ibuprofen.

Conclusions:

- Approximately half of the patients with chronic urticaria present NSAIDs hypersensitivity.
The percentage increases significantly in the case of patients who have autoimmune markers.

Ibuprofen is the anti-inflammatory drug most frequently incriminated for the occurrence of hypersensitivity reactions to nonsteroidal anti-inflammatory drugs, followed by aspirin. This can be explained through the much more frequent use it has as an anti-inflammatory drug.

### III.7. Etoricoxib safety set through drug challenge test

All patients with a history of NSAIDs hypersensitivity were subject to the drug challenge test with etoricoxib. Following the drug challenge drug only two patients out of 118 had a positive test, in the meaning of the occurrence of cutaneous eruption of the urticaria type. The remaining patients (116) tolerated well the total dose of 60 mg etoricoxib, without the occurrence of urticaria or angioedema. The test was monitored by calculating the urticaria activity score.

Etoricoxib seems to have a very good safety profile both in patients with autoreactive chronic urticaria and in patients with chronic idiopathic urticaria with negative autologous serum skin test [(b)Tudose AM, 2012].

**Conclusions:**

- The percentage of patients who tolerated etoricoxib was significantly higher as compared to that of patients with positive drug challenge test.
- The safety profile of etoricoxib from the statistical point of view achieved with the help of the McNemar test was excellent and statistically significant (p<0.0001)

### III.8. Efficiency of the thyroid hormone treatment in urticaria associated with autoimmune thyroiditis

The efficiency of thyroid hormone treatment was assessed on the group of patients with autoimmune urticaria and thyroiditis and who were evaluated endocrinologically as needing additional hormone therapy.

At the first treatment evaluation, after four weeks in which patients followed a treatment with large doses of H₁ antihistaminic drugs, 53.96% of the patients presented a significant improvement of the urticaria activity score (UAS). However, an importance percentage of patients maintained a high score (46.03%). The vast majority of these patients (79.31%) belonged to the group of patients with hypothyroidism, whether clinical or not (subclinical).
Patients with UAS score three and increased level of TSH (23 patients – sixteen with subclinical thyroiditis and seven with clinic thyroiditis) received additional treatment with 50 micrograms of L-thyroxine for four weeks at the recommendation of the endocrinology doctor.

Following treatment with L-thyroxine, 16 patients (69.56%) presented an improvement of the urticaria activity score. In other words, the beginning of the hormone treatment significantly improved the urticaria activity (score decrease from 3 points to one point). The other cases (30.43%) kept the same score, requiring a short treatment with systemic corticosteroids [(c)Tudose AM, 2012].

**Conclusions:**
- An important percentage of patients, despite the treatment with large doses of antihistaminic drugs kept a high urticaria activity score (46.03%).
- The vast majority of these patients belonged to the group with autoimmune markers.
- The association of the thyroid hormone supplement decreased the necessary antihistaminic treatment.
- There are contradicting reports on the results of hormone therapies. My study showed that in 75.86% of the patients treated with L-thyroxine, the urticaria activity score improved.

**III.9. Efficiency of antidepressants in urticaria associated with depression**

From among patients with urticaria and autoimmune thyroiditis there were selected patients (34 patients) who, following an antihistaminic treatment in large doses administered for four weeks reached urticaria activity score of one point.

All these patients received the depression symptoms questionnaire (validated for the Romanian population). It was applied according to the recommendations of the clinician psychologist. Following application of the questionnaire, 13 patients were identified with various degrees of depression (38.23%): six with mild depression, four with moderate depression and three with severe depression.

After four weeks of combined treatment (antihistaminic drug in small dose and mirtazapine 15 mg a day), no patient presented any urticaria eruption; moreover, eight interrupted the antihistaminic medication according to received indications (lack of urticaria wheals for a period exceeding five days).

After applying the questionnaire to set the degree of depression, all the patients presented a decrease of the “Z” score, and nine (69.23%) were diagnosed with a degree of depression lower than at the first visit. At the second evaluation of subjects, after four weeks of treatment, all patients registered a decrease of their depression score [(d)Tudose AM, 2012].
Conclusions:

- 38.23% of the patients with autoimmune urticaria presented various degree of depression.
- Mirtazapine improves the symptom score of depression while decreasing the “Z” score from the depression questionnaire.
- Depression as well as psychiatric co-morbidity could influence the evolution of chronic urticaria.
- The treatment of this pathology decreased the necessary antihistaminic medication.
- In the case of chronic urticaria with prolonged and severe evolution, with necessary antihistaminic therapy in large doses, the patients should undergo a psychological evaluation.

IV. Final conclusions

1. Autoimmune urticaria is more frequent in women, has a long evolution and partial answer to conventional H₁ antihistaminic medication.
2. Autoimmune thyroiditis is more common in terms of co-morbidity in the case of patients with autoimmune urticaria, the vast majority being euthyroid, for which reason functional thyroidal tests (free T3, free T4 and TSH) are not enough to detect a thyroid disease. Testing meant to detect tyreo-peroxydase antibodies must be conducted for all patients with positive autologous serum skin test.
3. The study provides original data on the incidence of the association of Hashimoto's thyroiditis with chronic urticaria among Romanian patients.
4. The study reveals that the frequency of hypersensitivity reactions to NSAIDs in patients with chronic urticaria was significantly higher in the case of patients who associated autoimmune markers, their occurrence being influenced by the positivity of their autologous serum skin test.
5. In practice, considering these results, patients with positive autologous serum skin test should be informed on the risk of hypersensitivity reactions to the administration of nonsteroidal anti-inflammatory drugs.
6. In what concerns the HLA profile of patients with autoimmune urticaria and thyroiditis associated with NSAID hypersensitivity, the antigens combination represented by:
   - HLA A₁, HLA B₄₄, HLA C₅ seems to influence significantly the occurrence of NSAIDs hypersensitivity and HLA-C₅ has a crucial role;
   - HLA-A₁₁, HLA-B₅₇ and HLA-C₃, particularly HLA-A₁₁.
7. In the group of patients with NSAIDs hypersensitivity, the most frequently met anti-inflammatory drug was ibuprofen followed by aspirin, ketoprofen and diclofenac.
8. Etoricoxib has a very good safety profile both in patients with chronic autoreactive urticaria and in patients with chronic idiopathic urticaria, with negative autologous serum skin test.
9. The beginning of the hormone treatment in patients who associate thyroid dysfunction or the antidepressant treatment in the case of patients who associate various degrees of depression can significantly improve urticaria activity score, while decreasing the necessary $H_1$ antihistaminic medication.
10. Mirtazapine, an antidepressant which also has poor $H_1$ antihistaminic effects, proved to be beneficial in improving urticaria symptoms, allowing the reduction of large $H_1$ antihistaminic doses or even its interruption.
11. Chronic urticaria remains a field to explore, the HLA profile playing probably a crucial role. One should not forget that an disease such as urticaria with multiple manifestations which influences the mood of the patients should benefit, from the first days of manifestation, from psychological counseling, sometimes even psychiatric evaluation and specific treatment.
12. The study of the HLA profile in the case of autoreactive urticaria associated with autoimmune thyroiditis is the first study conducted in Romania and aims to open the path for research on a large group of patients in order to set the genetically predictable factors for the occurrence of hypersensitivity to NSAIDs in patients with chronic urticaria.

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